

**ADVERSE GASTROINTESTINAL EFFECTS OF OVER-THE-COUNTER
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: A COST STUDY IN
TWO GAUTENG PUBLIC HOSPITALS**

Theshni Govender

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Medicine.

Johannesburg 2017

TABLE OF CONTENTS

ADVERSE GASTROINTESTINAL EFFECTS OF OVER-THE-COUNTER NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: A COST STUDY IN TWO GAUTENG PUBLIC HOSPITALS	i
DECLARATION	i
DEDICATION	ii
PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT	iii
PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT	iv
ACKNOWLEDGEMENTS.....	v
ABSTRACT	vii
CHAPTER 1. LITERATURE REVIEW	9
1.1 Introduction.....	9
1.2 Pain and Analgesia.....	9
1.3 NSAID analgesics.....	10
1.3.1 Mechanism of action of NSAIDs and UGIT adverse effects	10
1.3.2 Non-NSAID analgesics	12
1.3.3 Gastro protective agents (GPAs).....	13
1.4 Analgesics in South Africa	13
1.4.1 Legislation – SA.....	14
1.4.2 Patient perceptions of OTC NSAIDs – South Africa	15
1.4.3 Legislation - USA	17
1.4.4 Patient perceptions of OTC NSAIDs – United States of America	17
1.5 Risk Factors for NSAID induced UGIT complications.....	18
1.6 Pharmacoeconomics	20
1.7 References.....	21
CHAPTER 2. BACKGROUND OF THE STUDY	27
2.1 Purpose of the study	27
2.2 Context of the study	27
2.3 Problem Statement.....	28
2.3.1 Main problem.....	28
2.3.2 Sub problem.....	28
2.4 Significance of the study.....	28
2.5 Site of the study	29
2.5.1 Type of study	29
2.6 Definition of terms.....	30
2.7 Assumptions.....	30
CHAPTER 3. DRAFT MANUSCRIPT.....	31
3.1 Letter to the Editor – South African Pharmaceutical Journal (SAPJ).....	31
3.3 Manuscript accepted for publication by the South African Pharmaceutical Journal (SAPJ)...	41
Abstract	41
INTRODUCTION	43
METHODS	44

RESULTS.....	45
Figure 1: Study flow diagram	48
Table I. Demographic characteristics of patients using OTC NSAIDs vs patients using NSAIDs obtained on prescription (n=215).....	49
Table II: Incidence of analgesic use by 183 participants	52
Table III: Patterns of use of NSAIDS 215 respondents	54
Table IV: Details of the hospital admission, in-hospital treatment and calculation of costs of NSAID vs. Non- NSAID users.....	56
DISCUSSION	59
CONCLUSION	65
REFERENCES	65
APPENDIX 1.	71
CHAPTER 4. APPENDICES	73
APPENDIX 1. POSTER	73
APPENDIX 3. ETHICS APPROVAL	75
APPENDIX 4. RESEARCH PROTOCOL.....	76
<i>Cover Page</i>	76
<i>Literature Review</i>	77
<i>Hypothesis</i>	79
<i>Study objectives</i>	79
<i>Methods</i>	79
<i>Data analysis</i>	82
<i>Ethics</i>	82
<i>Budget/Funding</i>	82
<i>Limitations</i>	82
<i>Outcomes and benefits</i>	83
<i>References</i>	83
<i>Addendum 1 Retrospective audit results</i>	85
<i>Addendum 2: Clinical information recorded from patient files</i>	86
<i>Addendum 3: Questionnaire based survey</i>	88
<i>Addendum 4: Cost structure</i>	90
APPENDIX 5:Turn It In Report.....	93
APPENDIX 6: Explanatory notes for Turn It In Report.....	109

DECLARATION

I, Theshni Govender declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Theshni Govender

_____ day of _____ 2016 at _____

DEDICATION

You set an impossible standard and a flawless example.
Thank you for being my North Star.

For my husband Vinesh Reddy.

PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

Date	Name of Conference	Place	
April 2011	EAHPBA/ASSA-SAGES	Cape Town	Oral Poster Presentation
September 2012	International Surgical Week	Yokohama, Japan	Oral Poster Presentation
August 2015	ASSA/SAGES	Durban	Second Prize Best oral clinical paper
September 2015	School of Clinical Medicine Research Day	WITS, Johannesburg	Oral Paper Presentation
November 2015	Bert Myburgh Research Forum	WITS, Johannesburg	Oral Paper Presentation

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

Journal	Title/Authors	Year	Vol.	No.	Pages
South African Medical Journal	Over the counter sale of non-steroidal anti-inflammatories should be banned! (Abstract)	2011	101	4	274-275
World Journal of Surgery	Over the counter sale of non-steroidal anti-inflammatories should be banned! (Abstract)	2011	35	Supplement 1	S303

ACKNOWLEDGEMENTS

My supervisor Martin Brand who developed the original idea. His constructive criticism, advice, guidance and availability even throughout his overseas fellowship were invaluable.

Professor Jerome Loveland for affording me the time to complete this project and his assistance when stumbling blocks were encountered.

Professors KD Boffard, MG Veller and MD Smith for their support on behalf of the Department of Surgery.

I am indebted to Hermina Tau from the research department at Chris Hani Baragwanath Hospital, her dedication and diligent completion of the surveys made this project possible.

My colleagues and friends, Simon Dryden, Nosisa Sishuba, Devorah Wineberg and Amisha Maraj who facilitated seamless data collection at two hospitals simultaneously.

My family, for their encouragement and support.

I acknowledge, with the deepest reverence, each patient who shared their information with us and wished us well despite their illness.

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide. NSAIDs are increasingly available as an expanding range of over the counter (OTC) and prescription formulations. Straube et al, in a systematic review, report the mortality rate of individuals with UGIT bleeding/perforation using chronic oral NSAIDs is 1 in 5 due to gastrointestinal complications. The economic implications to a challenged, South African public healthcare system of treating serious, potentially preventable upper gastrointestinal complications attributed to the consumption of OTC NSAIDs does not appear to have been quantified.

A prospective observational study was conducted at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital over six months. Patients admitted to the surgical service with signs and symptoms of upper gastrointestinal bleeding were asked to complete a questionnaire-based survey. The cost to treat each patient was calculated.

Over the study period, 321 patients were admitted with upper gastrointestinal tract (UGIT) bleeding. The cost to treat patients included in the study sample (n=253) was R 10 463 668. Patients using NSAIDs (n=215) consumed 88% (R 9 194 698) of the expenditure, seven times more than the cost of treating patients who did not use NSAIDs (n=38; $p = 0.043$). Of the patients who used NSAIDS, 183 had purchased over the counter NSAIDs and consume 73% of the total expenditure.

The average cost to treat a patient with UGIT complications secondary to OTC vs. Prescription NSAIDs was not statistically significant. Due the higher number of

patients who used OTC NSAIDs the cost incurred to treat these patients was five fold more than to treat the patients taking prescription only NSAIDs.

We recommend strict enforcement of existing regulations governing the sale and marketing of OTC NSAIDs and intensive consumer education of their adverse effects, which may decrease the substantial financial cost to the public health system and morbidity to the South African population at risk.

Word count: 314

CHAPTER 1. LITERATURE REVIEW

1.1 Introduction

This section is a review of the literature relating to the core ideas and concepts relevant to the topic. There are two distinct contexts, research conducted in the first world and research in South Africa. Although relevant and crucial to development of healthcare in general, the varying socioeconomic population groups and environments studied are distinct and influence national policy and pharmacoeconomics in very different ways.

1.2 Pain and Analgesia

“Pain is one of the leading factors contributing to the global burden of disease as measured by years lived with disability” (Moore 2014). The World Health Organization analgesic ladder describes pain in mild, moderate and severe degrees (WHO 1996). Pain is also characterised by duration of symptoms and may be acute or chronic. Analgesics are drugs and medicines that effect relief of pain.

Analgesics can be divided into three broad categories:

- i) Non- opioids: Paracetamol, NSAIDs (non-selective and selective COX-1 and 2 inhibitors)
- ii) Opioids: Morphine, Fentanyl, Oxycodone, Codeine
- iii) Adjuvants: medicines that are primarily used for other indications but have analgesic effects. These include some antidepressant and antiepileptic drugs.

The choice of analgesic is dependent on:

- Type of pain
- Severity of pain
- Risk of adverse effects

1.3 NSAID analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide (Wilcox 2005), and in contrast with other analgesic drug classes are increasingly available as an expanding range of over the counter (OTC) and prescription formulations for the symptomatic relief of minor health ailments (Ajuoga 2008). Acetyl salicylic acid, ibuprofen, diclofenac and naproxen are commonly used non-selective NSAIDs obtainable OTC without prescription. Currently there are 41 analgesic molecules that are available on the market in 738 different products (Dyssel 2012). Acute, mildly painful conditions that are amenable to self-medication with an over the counter (OTC) non-steroidal anti-inflammatory drug (NSAID) include headache, dental pain, dysmenorrhoea, minor musculoskeletal injuries and pain associated with upper respiratory tract infections.

1.3.1 Mechanism of action of NSAIDs and UGIT adverse effects

NSAIDs relieve pain by inhibiting prostaglandin synthesis via prostaglandin cyclooxygenase (COX). COX exists in two forms. The COX-1 enzyme is involved in maintaining normal, protective gastric function and COX-2 is up regulated in areas of inflammation. Individual compounds have varying affinities for COX-1 and COX-2. OTC NSAIDs are non-selective and inhibit both forms of COX. They are toxic to the gastric mucosa, causing injury by local irritative as well as systemic effects.

According to Bidaut-Russell (2001), NSAIDs alter normal gastric defence mechanisms by:

- Inhibition of prostaglandin synthesis, they decrease the secretion of mucus and bicarbonate
- Inhibiting regulation of acid secretion and mucosal proliferation
- Decreasing local blood flow
- Compromising platelet and coagulation mechanisms

NSAID use also has a well-reported array of adverse effects extending to the cardiovascular, renal and hepatic systems.

Singh (1998) categorised the adverse UGIT effects of NSAIDs into:

- i) The 'nuisance' or mildest UGIT symptoms include heartburn, nausea, vomiting, abdominal pain and dyspepsia
- ii) More severe adverse effects these extend to endoscopically visible gastric mucosal ulceration
- iii) Serious UGIT complications requiring hospitalisation. These complications are recognized as clinically significant upper and lower gastrointestinal events (CSULGIE's) of which upper gastrointestinal tract (UGIT) bleeding is the most common (Moore 2013).

The aggregate risk of UGIT bleeding or perforation among NSAID users is 2.7 to 5 times that of non-users (Straus 2001, Rodriguez 2007). Individual NSAIDs display different risks for resultant UGIT bleeding. Ibuprofen and diclofenac are associated with the lowest risk for GI toxicity. Moderate risk is associated with indomethacin, naproxen and aspirin (acetyl salicylic acid)(Bidaut-Russell 2001). Hernandez-Diaz (2000) demonstrated that this is related to the half-life of the drug and length of exposure. Bidaut-Russell (2001) note that selective COX-2 inhibitors are associated

with significantly fewer clinically important adverse upper GI events compared to naproxen and that combinations of more than one NSAID appear to be exceptionally toxic in susceptible individuals.

Despite the potential adverse effects, OTC NSAID use is seven-times greater than that of prescribed NSAIDs (Wilcox 1994). A systematic review of 61067 cases, investigated the mortality rate of UGIT bleeding or perforation. Data published since 1997 indicate that mortality is 1 in 13 overall but increases to 1 in 5 for patients exposed to NSAIDs. (Straube 2009)

1.3.2 Non-NSAID analgesics

Paracetamol (synonymous with acetaminophen) is an analgesic and anti-pyretic but has no anti-inflammatory action. Its mechanism of action is incompletely understood and has dose dependent (above 1g) inhibition of the COX-2 enzyme. Brune (2009) states that long-term use of paracetamol results in most of the negative effects typical of NSAIDs including hypertension, cardiac infarction, renal failure and gastrointestinal toxicity.

Despite the many cases of death due to overdoses and toxicity, paracetamol remains the most commonly used medication in the USA and Europe (Aghababian 2010). Paracetamol and acetyl salicylic acid have more adverse drug reactions than some NSAIDs that have recently been removed from prescription-only use. Brune (2009) goes on to recommend that (acetyl salicylic acid) and paracetamol not be available OTC to limit the incidence of death and severe adverse drug reactions.

1.3.3 Gastro protective agents (GPAs)

GPAs substantially reduce morbidity and mortality in patients using selective or non-selective long term NSAIDs and acetyl salicylic acid. Moore (2014) states that proton pump inhibitors (PPI) and high-dose histamine-2 receptor antagonists (H2RA) provided similar gastro protection, with no conclusive evidence of greater PPI efficacy compared with high-dose H2RA.

1.4 Analgesics in South Africa

The Medicines Control Council (MCC) is the medicines regulatory authority in South Africa. The MCC is a statutory body established in terms of the Medicines and Related Substances Control Act (Act 101 of 1965) that governs the manufacture, distribution, sale and marketing of medicines. The prescribing and dispensing of medicines is controlled through the determination of schedules for various medicines and substances. (www.mccza.com Accessed 6 October 2016)

The South African Ministry of Health introduced an Essential Drug Programme in 1996. The Essential Medicines List (revised 2014) and Standard Treatment Guidelines for primary health care were the products of this initiative. Essential medicines are defined as “those that satisfy the priority health care needs of the population” and this is one of the eight elements of primary health care as outlined in the Declaration of Alma-Ata (WHO 1978). “The idea behind essential medicines is

that a list of a few selected medicines will help meet the priority health needs of populations, resulting in better health care, improved medicine management, better use of financial resources and greater access to care” (Quick 2003).

The South African Essential Medicines List (SAEML 2014) proposes ibuprofen as an alternate analgesic to paracetamol in the first line management of pain. No alternative is suggested for ibuprofen, and consequently the use of NSAIDs is common in South Africa.

1.4.1 Legislation – SA

Bennin (2015) emphasises that legislation is not strictly enforced in South Africa where non-selective NSAID preparations are readily available in government clinics, private pharmacies, grocery stores, ‘spaza shops’, stands at transportation sites and a myriad other formal and informal outlets with limited if any accompanying patient information.

The South African Medicines Control Council (MCC) legally requires that OTC medication be accompanied by packaging that includes three major mechanisms to provide the end user with access to dosage instructions and health risk information. All three should be produced by the manufacturer and approved by the MCC.

These are:

- i) Container label – basic information about the medication
- ii) Medication insert – scientific information for health professionals

iii) Patient Information leaflet – simple information for the end user in layman's terms (South African National Government. Medicines and related substances act. Amended 2003)

Bennin (2015) states that in government health facilities and some pharmacies, OTC analgesics are cost-effectively repackaged in re-sealable plastic packets with either preprinted labels or hand-written dosage instructions. 'These repackaged medications are provided for free at government health facilities but are also sold cheaply and often in bulk to consumers at pharmacies'. Bennin's (2015) survey also highlights that this form of information is not effective in areas where health literacy and socioeconomic status are low, regular and standardized verbal instructions in the appropriate language and pictorial information may be more useful.

1.4.2 Patient perceptions of OTC NSAIDs – South Africa

In South Africa 84% of the population do not have medical insurance, and studies have shown that many patients deem self-funded primary health care visits as expensive as well as inconvenient (Mayosi 2014). South African consumers have also been shown to perceive generic medicines, obtained at no cost from public healthcare providers, as inferior and of poor quality (Patel 2012). This places limitations on national medicine policies and may influence consumers to purchase specific, preferred brands of analgesics. NSAID use in the South African public healthcare system does not mirror that of the private healthcare sector (Dyssel 2012). Selective cyclooxygenase inhibitors are a group of NSAIDs, which have a significantly lower incidence of UGIT side effects. Gastroprotective agents (GPAs) that are available OTC are not always available at the same vendors that sell OTC NSAIDs and consumers may not be aware of the necessity to use GPAs to prevent

adverse effects of OTC NSAIDs. Both GPAs and selective COX-inhibitors are not included in the SA Essential Medicines List; consequently they are not easily available and financially out of reach of the majority of South Africans.

Grand-Pa™ Headache powder (acetyl salicylic acid-paracetamol-caffeine) is sold only in Southern Africa. As at 2015, it leads the analgesic market with a 45.6% market share competing with Panado™ (paracetamol) with a brand retail value share of 20.7%, Disprin™ (acetyl salicylic acid) with 17.9% market share and Compral with a 7.1 % market share (Agola 2016) These brands are household names with a historical role in influencing customer choice, are widely available in both formal and informal retailers and are trusted and supported by strong marketing campaigns.

Continental Outdoor Media is an advertising company that published their 2013 marketing strategy for Grand-Pa™ in Shoshanguve, an informal settlement 25km north of Pretoria. According to data from Nielsen Research, Grand-Pa™ is a market leader in the analgesics market contributing 39% to the total category sales value. Its main competitors are Disprin™ (Reckitt Benckiser), Anadin™ (Pfizer), Panado™ and Compral™ (both Tiger Brands) – these collectively contributing 54% to the total category sales value.

The impact of an outdoor advertising campaign demonstrated strong impact on sales of Grandpa powders that despite introduction of the new tablet formulation (not available at the time of the study), was the driver of overall brand growth. The main volume gain was captured from Panado and a total sales increment of 3.5 % was gained with one well-placed billboard.

1.4.3 Legislation - USA

In April 2009, to improve public safety and awareness, the United States Food and Drug Administration issued a ruling requiring all NSAID manufacturers to list comprehensive, clearly visible warnings on all NSAID packaging, especially informing consumers about the dangers of UGIT bleeding, the most commonly reported adverse drug event in the country. The compliance date was set for April 2010, giving manufacturers one year to modify existing packaging and labelling to meet the new specifications. The total monetised benefit of illness and death prevented respectively would be \$ 5.6 million to \$ 16.8 million annually. The drug industry would incur the one-time cost of the ruling of \$ 32 million in the first year. Hence the benefits of the ruling more than offset the monetary cost (Federal Register 2009).

1.4.4 Patient perceptions of OTC NSAIDs – United States of America

The Roper Survey (performed for the American Gastroenterological Society) and the National Consumer League Survey were analysed by Wilcox (2005). Combined, 9062 people in the United States of America (USA) were surveyed. The results indicate that NSAIDs are perceived by consumers to be safe drugs and are frequently taken inappropriately and potentially dangerously. A recommendation for education directed toward physicians and patients was concluded. Ibuprofen was the most commonly used OTC NSAID.

1.5 Risk Factors for NSAID induced UGIT complications

- Age

Advanced age itself has been shown to be an independent risk factor for UGIT bleeding as well as the most widely reported risk factor for UGIT bleed-associated mortality (Rahme 2001). Approximately 40-60% of NSAID consumers are over 60 years of age (Gurwitz 1991), and up to 95% of elderly patients taking NSAIDs may obtain their medication OTC (Cebollero-Santamaria 1999).

In the Western world, the proportion of older patients suffering from UGIT bleeds has increased over recent years, mostly due to increased life expectancy and widespread NSAID use (Rahme 2001).

South Africa's population older than 60 years of age has increased from 2.8 million (1996) to 4.1 million (2011) with projections of 7 million by 2030. Current socio-economic assessments estimate that 40% of the elderly live in poverty, 38% rely on chronic medication and 28 % have no formal education (Lehlohlhla 2014).

In view of the fact that the risk of an UGIT bleed increases from 1.65 per 100 000 in patients <65 years to 5.7 per 100 000 in those >65 years and 12.7 per 100 000 in patients >75 years of age (Hansen 1996, Gabriel 1991) together with social and economic deficiencies the potential cost to SA healthcare is significant.

- Co-morbidities

Epidemiological studies have demonstrated non-gastrointestinal comorbidities and a history of previous UGIT ulceration as independent risk factors for UGIB (Crooks 2013).

- HIV

Pain is a common symptom in people living with HIV and AIDS, occurring in 60% to 98% of patients in South Africa (Norval 2004). The South African Essential Medicines List (SA EML) treatment protocol for management of adult HIV and AIDS related pain recommends paracetamol and/or ibuprofen first line treatment.

A study conducted at a primary health care facility in the city of Tshwane determined that ibuprofen was prescribed for 44% of patients and aspirin (acetyl salicylic acid) for 18% (Maree 2013). In addition, 84% of prescriptions contained suboptimal drug dosages and an insufficient quantity of tablets to sustain the patient to the next appointment, consequently more than 25% of the sample population used OTC analgesia.

In a study conducted at an HIV clinic in Houston Texas OTC NSAIDs accounted for 38% of the most commonly used medications (Ajuoga 2008). All patients taking NSAID's were prescribed gastro protective agents (GPAs) and the reported adverse drug reactions with concurrent antiretroviral treatment were 16 %, most were type II drug reactions.

- *Helicobacter pylori*

H.pylori is ubiquitous in Africa and often is acquired in childhood. Infection with the organism has been shown to exacerbate severe gastric mucosal injury in patients using oral NSAIDs. Segal (2001) demonstrated prevalence of a virulent strain in the Soweto population however the upper GI pathology had a variable, often low distribution in sub-Saharan Africa that did not parallel *H.pylori* prevalence in the population.

1.6 Pharmacoeconomics

The cost of NSAID induced gastropathy has been best quantified in the elderly, a population group that on their own exhibit a high baseline rate of gastrointestinal bleeding (Smalley 1995) and are the highest consumer group of NSAIDs (Ahmed 2012). Medical costs to treat the complications of UGIT bleeds in the elderly who use prescribed NSAIDs in the USA have been estimated at over \$ 4 billion per year, and the annual cost attributed to lost work productivity and care exclusive of treatment expenditure amount to \$ 5.65 billion (Kendall 1993). A limitation of these cohort healthcare cost studies is that OTC medication use is not included as these are paid for by the patient, hence these costs are not captured in clinical billing databases.

Vonkemann (2007) conducted an observational cost-of-illness study in the Netherlands including hospitalised patients with serious NSAID-related UGIT complications. The total direct annual medical cost was estimated to be € 42 754375 (95% CI) and within range of two other Dutch studies (Herings 2001, Chevat 2001) none of these studies examined costs incurred by OTC NSAIDs.

1.7 References

- Aghababian RV. (2010) *Essentials of emergency medicine*. Jones & Bartlett Publishers. p. 814.
- Agola NO, Hunter A. (2016) Inclusive innovation for Sustainable Development: Theory and Practice. Springer. P.132
- Ahmed A, Stanley AJ. (2012) Acute Upper Gastrointestinal Bleeding in the Elderly. *Drugs Aging*. 29(12), 933–40.
- Ajuoga E, Sansgiry SS, Ngo C, Yeh RF. (2008) Use/misuse of over-the-counter medications and associated adverse drug events among HIV-infected patients. *Research in Social and Administrative Pharmacology*. 4(3), 292–301.
- Bennin F, Rother H. (2015) “But it’s just paracetamol”: Caregivers’ ability to administer over-the-counter painkillers to children with the information provided. *Patient Education and counseling*. (98), 331-337.
- Bidaut-Russell M, Gabriel SE. (2001) Adverse gastrointestinal effects of NSAIDs: Consequences and costs. *Best practice & Research Clinical Gastroenterology*. 15(5), 739-753.
- Bornman MS. (2009) Organ-Specific warnings; Internal Analgesia, [Antipyretic](#) and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph. Final rule. Federal Register .74(81), 19385 – 19409.

Brune K, Hinz B, Otterness I. (2009) Aspirin and Acetaminophen: Should they be available over the counter? *Current Rheumatology Reports*. (11), 36-40.

Cebollero-Santamaria F, Smith J, Gioe S, Frank T, Mc Call R, Airhart J et. Al. (1999) Selective outpatient management of upper gastrointestinal bleeding in the elderly. *American Journal of Gastroenterology*. 94(5), 1242–7.

Chevat C, Pena BM, Al MJ. (2001) Healthcare resource utilisation and costs of treating NSAID-associated gastrointestinal toxicity: a multinational perspective. *Pharmacoeconomics*. 19(6), 17-32.

Continental Outdoor Media Grandpa Study.(2013) How efficient was the Grand-Pa™ billboard in Shoshanguve?

www.continentaloutdoor.com/images/.../Continental-outdoor-media-Grandpa-Study.pdf

[Accessed online 19 October 2016]

Crooks CJ, West J, Card TR. (2013) Comorbidities Affect Risk of Nonvariceal Upper Gastrointestinal Bleeding. *Gastroenterology*. 144(7), 1384–1393.

Dyssel N. (2012) The analgesic market in South Africa – A critical review of contributing growth factors over the past four years.[Dissertation] University of Stellenbosch.

Euromonitor. (2014) Analgesics in South Africa Market Research Report.

<http://www.euromonitor.com/analgesics-in-south-africa/report>

[Accessed online 19 January 2015]

Gabriel SE, Jaakkimainen L, Bombardier C. (1991) Risk for Serious Gastrointestinal Complications Related to Use of Nonsteroidal Anti-inflammatory Drugs: A meta-analysis. *Annals of Internal Medicine*. 15;115(10), 787-796.

Gurwitz JH, Avorn J. (1991) The Ambiguous Relation between Aging and Adverse Drug Reactions. *Annals of Internal Medicine*. 1;114(11), 956.

Hansen JM, Hallas J, Lauritsen JM, Bytzer P. (1996) Non-Steroidal Anti-Inflammatory Drugs and Ulcer Complications: a Risk Factor Analysis for Clinical Decision-Making. *Scandinavian Journal of Gastroenterology*. 31(2),126–130.

Herings RMC, Klungel OH. (2001) An epidemiological approach to assess the economic burden of NSAID-induced gastrointestinal events in The Netherlands. *Pharmacoeconomics*. 19(6),655-665.

Hernandez-Diaz S, Garcia-Rodriguez LA. (2001) Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *American Journal of Medicine*. 110(3A), 20S-27S.

Kendall BJ, Peura DA. (1993) NSAID associated gastrointestinal damage and the elderly. *Practical Gastroenterology*. (17), 13-20.

Lehohla P. (2014) Census 2011 – Profile of older persons in South Africa. Statistics South Africa. [Online] Report No.03-01-60.

Available from: www.statssa.gov.za

[Accessed 19 January 2015]

Maree JE, Dreyer Wright SC, Makua MR. (2013) The Management of HIV- and AIDS-Related Pain in a Primary Health Clinic in Tshwane, South Africa. *Pain Management Nursing*.14(2), 94–101

Mayosi BM, Benatar SR. (2014) Health and Health Care in South Africa — 20 Years after Mandela. *New England Journal of Medicine*. 371(14):1344–53.

Medicines Control Council website. www.mccza.com [Accessed online 19 October 2016]

Moore RA, Derry S, Simon LS, Emery P. (2014) Nonsteroidal Anti-inflammatory drugs, gastroprotection and benefit risk. *Pain Practice*. (4), 378-395.

Norval DA.(2004) Symptoms and sites of pain experienced by AIDS patients. *South African Medical Journal*. 94(6), 450–454.

Patel A, Gauld R, Norris P. Rades.(2012) Quality of generic medicines in South Africa. Perceptions versus Reality – A qualitative study. *BMC Health Services Research*. (12), 297

Quick JD. (2003) Essential Medicines twenty-five years on: closing the access gap. *Health and policy planning*.18(1), 1-3.

Rahme E, Joseph L, Kong SX, Watson DJ, LeLorier J. (2001) Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients. *British Journal of Clinical Pharmacology*.52(2),185–92.

Rodriguez LAG, Tolosa LB. (2007) Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology*. (132),498-506.

Standard Treatment Guidelines and Essential Medicines List for South Africa. Fifth edition. Pretoria. The National Department of Health 2014. Chapter 12. [Online] www.kznhealth.gov.za/pharmacy/edlphc2014a.pdf [Accessed 17 October 2016]

SA National Government. Medicines and related substances act. (Act 101 of 1965.Amended in 2003)

Segal I, Ally R, Mitchell H. (2001) *Helicobacter pylori* – An African perspective. *QJM* 94(10):561-5

Singh G.(1998) Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *American Journal of Medicine*. **105**:31s-38s

Smalley WE, Ray WA, Daugherty JR, Griffin MR. (1995) Nonsteroidal anti-inflammatory drugs and the incidence of hospitalisations for peptic ulcer disease in elderly persons. *American Journal of Epidemiology*. (141), 539-545.

Straube S, Tramer MR, Moore RA, Derry S, McQuay HJ. (2009) Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. *BMC Gastroenterology*.(9),41.

Straus WL, Ofman JJ. (2001) Gastrointestinal toxicity associated with anti-inflammatory drugs. *Gastroenterological Clinics of North America*. 30(4),895–920.

Vonkemann HE, Klok, RM, Postma MJ, Jacobus RBJ, Brouwers JRBJ, Vna de Laar MAFJ. (2007) Direct medical costs of serious gastrointestinal ulcers among users of NSAIDs. *Drugs Aging*. 24(8), 681-690.

World Health Organization (WHO). (1978). Declaration of Alma-Ata, International conference on primary health care, Alma Ata, USSR, 6-12 September 1978 .

Available online: http://www.who.int/hpr/NPH/docs/declaration_almaata.pdf

[Accessed 21 July 2012]

[World Health Organisation \(1996\) Cancer Pain Relief 2nd Edn. \(World Health Organisation, Geneva, Switzerland\)](#)

Wilcox CM, Shalek KA, Cotsonis G.(1994) Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. *Archives of Internal Medicine*. 10;154(1),42–46.

Wilcox CM, Cryer B, Triadafilopoulos G.(2005) Patterns of use and public perception of over the counter pain relievers: Focus on nonsteroidal anti-inflammatory drugs. *The Journal of Rheumatology*.32(11),2218-2224.

CHAPTER 2. BACKGROUND OF THE STUDY

2.1 Purpose of the study

The purpose of the study is to determine the monetary cost to healthcare in the treatment of preventable UGIT complications in patients who use NSAIDs obtained OTC. The research aims to establish patterns of OTC NSAID use and highlight existing regulations governing analgesic use and distribution in South Africa that may not be enforced or practiced.

2.2 Context of the study

In 2010, the proportion of patients admitted to the surgical wards with UGIT complications secondary to the use of OTC NSAIDs appeared considerable. The UGIT complications that patients suffered were both potentially completely preventable and potentially fatal. Advertising and marketing campaigns of these products were extensive and included the immediate vicinity of public hospitals throughout Gauteng. These drugs were readily available from informal and formal vendors, including the canteen within the hospital and appeared to have a strong historic brand appeal to consumers. The hypothesis put forth was that if a significant cost to healthcare, incurred for treatment of a preventable condition, could be demonstrated that existing regulation around the sale, advertising and marketing of OTC NSAIDs could be more strictly enforced.

A retrospective audit of medical records of all patients admitted to the surgical wards at Charlotte Maxeke Academic Hospital during 2010 with UGIT complications was

performed. This audit revealed that 170 patients were admitted with UGIT complications in one year and 24% of these patients obtained their NSAIDs OTC. A direct cost to healthcare of R 1 748 748 (22% of the total cost to treat all UGIT complications) was spent to treat these complications. This cost was substantial. (Appendix 2. Poster)

The challenges encountered in the audit were: inconsistently recorded information on patient discharge summaries and difficulty accessing patient data archived on microfiche.

The way forward was to prospectively collect the data to ensure accuracy and consistency.

2.3 Problem Statement

2.3.1 Main problem

Prospectively establish the patterns of NSAID use in the patient population admitted to the surgical service with UGIT complications.

2.3.2 Sub problem

Establish the cost incurred by the public health system in treating patients who use OTC NSAIDs compared to those who obtain NSAIDs on prescription.

2.4 Significance of the study

The study aims to provide insight into potentially preventable, surgically managed UGIT complications treated in the public health care sector in South Africa. It aims to

fill a gap in the research where costs incurred by challenged public health systems in treating such complications have not yet been quantified.

The value of the study would be to identify factors that may contribute toward stricter enforcement of existing South African Medicines Control Council (MCC) regulations and increased emphasis on consumer education. It is conceivable that this insight would provide public health role players with new avenues to decrease surgical morbidity and enhance quality of life for patients while simultaneously reducing government expenditure on treatment costs for preventable conditions.

2.5 Site of the study

- The study will be conducted at the two largest public hospitals in the Gauteng province. Chris Hani Baragwanath Academic hospital is the largest hospital in the southern hemisphere and the third largest hospital in the world and Charlotte Maxeke Johannesburg Academic Hospital.

2.5.1 Type of study

- The study aims to follow a prospective cohort study type of design.

2.6 Definition of terms

- Non steroidal anti inflammatory drugs (NSAIDs)

Class of drugs that display antipyretic, analgesic and anti-inflammatory effects.

- Over the counter (OTC)

With specific reference to medication purchased, without prescription, from formal or informal retailers, who may or may not possess a dispensing license.

- Upper gastrointestinal tract (UGIT)

The alimentary canal from oral mucosa to the Ligament of Treitz (duodenojejunal junction)

2.7 Assumptions

The outcome of this study is contingent on a few assumptions:

- The respondents possess the information and freedom to complete the surveys in an unbiased manner.
- The respondents are free to opt out of the survey if they do not wish to disclose any information that they deem sensitive.

CHAPTER 3. DRAFT MANUSCRIPT

3.1 Letter to the Editor – South African Pharmaceutical Journal (SAPJ)

Thank you for considering this original research manuscript for publication.

The paper is titled “Adverse gastrointestinal effects of over the counter non-steroidal anti-inflammatory drugs: A cost study in two Gauteng public hospitals”.

The research was conducted prospectively over six months using a questionnaire-based survey to gather demographic and clinical data from patients presenting to the surgical service with upper gastrointestinal bleeding.

We examined the hospital admission records of each patient and performed a cost calculation to assess the expenditure by state hospitals in treating a potentially preventable complication in those patients taking NSAIDs obtained OTC.

The significant cost is relevant to the challenged South African public health care system and would be of interest to community pharmacists, doctors and pharmacoeconomists.

I confirm that this is an original article and has not been published or is under consideration for publication elsewhere.

3.2 SAPJ Author Guidelines

Electronic, online submissions at www.sapj.co.za/authors are preferred.

All new users to the website must register first. Once registered, simply log in, click on "Information for authors" and then on "START SUBMISSION PROCESS". An easy 5-step process guides you through the uploading of your manuscript.

All manuscripts must be submitted in MS Word® (not RTF) format using Times New Roman font size 10 and single-spacing. The author must always retain a copy. All the named authors must have approved the final manuscript. Pages should be numbered consecutively in the lower right corner.

The following contributions are accepted:

Original research

(3200-4600 words)(4-6 pages). Structured abstract (Background, Methods, Results and Conclusion(s)).

Pharmacy-orientated clinical reviews

First part:

1-2 pages clinical review of the condition and rationale for selecting drugs.

Second part:

2-3 pages on the role of the pharmacist (referral criteria/warning signs, dispensing notes (compliance issues, drug interactions etc.), monitoring a treatment response, side-effect management, SAE reporting, generic substitution with particular drug classes). (3200-4600 words)(4-6 pages)

Scientific review articles

Reviews in the following disciplines – pharmaceuticals, pharmacology, pharmaceutical chemistry, pharmacy practice, social and administrative pharmacy. (1800-2400 words)

Short clinical updates

(1800 words)(3 pages) Short clinical review to update pharmacist on new developments of a condition – clinically or in the therapeutic approach.

Evidence-Based-Pharmacy-Initiated Pharmacotherapy (EBPIP)

(1800-2400 words)(3-4 pages) Over the counter medication as well as prescription only medication. Important to include clear guidelines on clinical presentations and rationale for drug selection. For OTC medication, must include a section on “when to see your doctor..”

Pharmacovigilance

(SAE reporting, clinical articles on identifying adverse drug reactions, reviews on side-effect management (choosing a drug with best side-effect profile (For example Antidepressants and erectile dysfunction – what the pharmacist should know. Myalgia and statins – what pharmacists should know and tell their patients.)

Pharmaco-economics

Reviews on the cost-effectiveness of therapy. (2 400 words)(3-4 pages)

Regulations/Policy

(1800-2400 words)

Case studies

A pharmacy case study. (1 200 words)(2 pages)

Critical appraisals of clinical trials

(300 word trial summary and 300 word commentary)(<600 words in total including references)

Scientific Letters

(2400 words)(3-4 pages)

Letters to the Editor

(400-800 words)(1 page)

Open Forum/Opinion paper

(2400 words)(4 pages maximum)

Format

All manuscripts must be submitted in UK English, typed in MS Word, Times New Roman, font size 10. All articles must be proof read by a language specialist or a colleague proficient in English before submission.

Title page

All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; name, postal address, e-mail address and telephonic contact details of the corresponding author and at least 5 keywords.

Abstract

All articles should include an abstract. The structured abstract for an Original Research article should be between 200-230 words and should consist of four

paragraphs labeled Background, Methods, Results, and Conclusions. It should briefly describe the problem or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results. The abstracts for other types of articles should be no longer than 230 words and need not follow the structured abstract format.

Keywords

All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of Index Medicus when available and appropriate. Key words are used to index the article and may be published with the abstract.

Web-long, paper-short policy for original articles

The full text of original research articles will be available online only. The structured abstract (up to 230 words) will be published in hardcopy and the reader will be referred to the open access website to print the full copy if required.

Acknowledgments

In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References

Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript). Please do not use brackets or do not use the footnote function of MS Word. In the *References* section, references must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically. The style for references should follow the format set forth in the *Uniform Requirements*

for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org>) prepared by the *International Committee of Medical Journal Editors*.

Abbreviations for journal titles should follow *Index Medicus* format. Authors are responsible for the accuracy of all references. Personal communications and unpublished data should not be referenced. If essential, such material should be incorporated in the appropriate place in the text. List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al". When citing URLs to web documents, place in the reference list, and use the following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:

1. London L, Baillie R. Notification of Pesticide Poisoning: Knowledge, Attitudes and Practices of Doctors in the Rural Western Cape. *S A Fam Pract* 1999;20(1):117-20.
2. FDA Talk Paper:
<http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01151.html> (Accessed 04/10/2002).

More sample references can be found at:

http://www.nlm.nih.gov/bsd/uniform_requirements.html

Tables

Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should include a clear descriptive title on top and numbered in Roman numerals (I, II, etc.) in order of its appearance as called out in

text. Tables must be inserted in the correct position in the text (not at the end).

Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations. For footnotes use the following symbols, in sequence:

*,†,‡,§,||,**,††,‡‡

Figures

All figures must be inserted in the appropriate position of the electronic document. Symbols, lettering, and numbering (in Arabic numerals e.g. 1, 2, etc. in order of appearance in the text) should be placed below the figure, clear and large enough to remain legible after the figure has been reduced. Figures must have clear descriptive titles.

Photographs and images

If photographs of patients are used, either the subject should not be identifiable or use of the picture should be authorised by an enclosed written permission from the subject. The position of photographs and images should be clearly indicated in the text. Electronic images should be saved as either jpeg or gif files. All photographs should be scanned at a high resolution (300dpi, print optimised). Please number the images appropriately.

Permission

Permission should be obtained from the author and publisher for the use of quotes, illustrations, tables, and other materials taken from previously published works, which are not in the public domain. The author is responsible for the payment of any

copyright fee(s) if these have not been waived. The letters of permission should accompany the manuscript. The original source(s) should be mentioned in the figure legend or as a footnote to a table.

Review and action

Manuscripts are initially examined by the editorial staff and are usually sent to independent reviewers who are not informed of the identity of the author(s). When publication in its original form is not recommended, the reviewers' comments (without the identity of the reviewer being disclosed) may be passed to the first author and may include suggested revisions. Manuscripts not approved for publication will not be returned.

Ethical considerations

Papers based on original research must adhere to the Declaration of Helsinki on "Ethical Principles for Medical Research Involving Human Subjects" and must specify from which recognized ethics committee approval for the research was obtained.

Conflict of interest

Authors must declare all financial contributions to their work or other forms of conflict of interest, which may prevent them from executing and publishing unbiased research. [Conflict of interest exists when an author (or the author's institution), has financial or personal relationships with other persons or organisations that inappropriately influence (bias) his or her opinions or actions.]*

*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA 2001; 286(10)

The following declaration may be used if appropriate: "I declare that I have no

financial or personal relationship(s) which may have inappropriately influenced me in writing this paper."

Submissions and correspondence

All submissions and correspondence regarding manuscripts should be addressed to Lorraine Osman, E-mail: lorraine@pharmail.co.za or an electronic copy on CD may be sent to, The Editor, SAPJ, PO Box 26039, Arcadia, 0007

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in Microsoft Word document file format.
3. All URL addresses in the text (e.g., <http://pkp.sfu.ca>) are activated and ready to click.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); and all tables and figures are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the [Author Guidelines](#), which is found in About the Journal.
6. Electronic images are saved as either jpeg or gif files. All photographs were scanned at a high resolution (300dpi, print optimised) and saved/numbered appropriately corresponding with the text.
7. All tracking changes in the document must have been accepted before sending it to SAPJ.

8. Have you asked a colleague or language expert to proofread your final manuscript?
9. All supplementary files such as survey instruments or scanned photographs are separated from the main text and will be uploaded as supplementary files.
10. In the case of a research paper, prior approval has been obtained from a research ethics committee, and this fact is declared in the methods section of the manuscript.

Copyright Notice

By submitting manuscripts to SAPJ, authors of original articles are assigning copyright to Medpharm Publications (Pty) Ltd. Authors may use their own work after publication without written permission, provided they acknowledge the original source. Individuals and academic institutions may freely copy and distribute articles published in SAPJ for educational and research purposes without obtaining permission.

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party.

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide. Unlike other classes of drugs, NSAIDs are increasingly available as an expanding range of over the counter (OTC) and prescription formulations. Straube (2009) states in a systematic review that the mortality rate of individuals with upper GIT bleeding or perforation and using chronic oral NSAIDs is 1 in 5 due to gastrointestinal complications. The economic implications to a challenged, South African public healthcare system of treating serious, potentially preventable upper gastrointestinal bleeds attributed to the consumption of OTC NSAIDs does not appear to have been quantified.

Method

A prospective observational study was conducted at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital over a six-month period

Patients admitted to the surgical service with signs and symptoms of upper gastrointestinal bleeding were asked to complete a questionnaire-based survey. Clinical details were collected from patient files after they were discharged. The cost to treat each patient was calculated.

Results

Over the study period, 321 patients were admitted with upper gastrointestinal tract (UGIT) bleeding. The total cost to treat patients included in the study sample (n=253)

was R 10 463 668. Patients using prescription and OTC NSAIDs (n=215) consumed 88% (R 9 194 698) of the expenditure, seven times more than the cost of treating patients who did not use any NSAIDs (n=38; $p = 0.043$). Of the 215 patients who used NSAIDs, 183 had purchased over the counter NSAIDs and consumed 73% of the total expenditure.

Conclusion

The cost to treat patients with UGI bleeds over six months is in excess of ZAR 10 million. Due the higher number of patients who used OTC NSAIDs the cost incurred to treat these patients was five fold more than to treat the patients taking prescription only NSAIDs.

Key words: over the counter, analgesics, non-steroidal anti-inflammatory drugs, upper gastrointestinal bleeding, cost

Word count : 297

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide ¹ and in contrast to other analgesic drug classes, are increasingly available as an expanding range of over the counter (OTC) and prescription formulations.² Currently there are 41 analgesic molecules available on the South African market in 738 different product formulations.³

The NSAIDs are perceived to be safe drugs by the general public and consequently OTC NSAID use is seven-times greater than that of prescribed NSAIDs⁴. However NSAID use is associated with significant gastrointestinal tract complications. The aggregate risk of UGIT complications among NSAID users is 2.7 to 5 times that of non-users^{5, 6} A systematic review of 61 067 cases investigated the mortality rate associated with UGIT bleeding or perforation. Data published since 1997 indicate that mortality is 1 in 13 overall but increases to 1 in 5 for patients with upper GIT bleeds or perforations exposed to NSAIDs⁷.

In 2009, in an attempt to improve public awareness, the United States Food and Drug Administration issued a ruling requiring all NSAID manufacturers to list comprehensive warnings on all NSAID packaging with specific reference to UGIT bleeding, the most commonly reported adverse drug event in the country.⁸

Similar legislation does not exist in South Africa where non-selective NSAID preparations are readily available in pharmacies, grocery stores and a myriad of other formal and informal outlets with limited if any accompanying patient information. In the South African context, the direct financial implications to the public healthcare system of treating potentially preventable UGIT bleeding complications, attributed to the consumption of OTC NSAIDs does not appear to have been quantified.

METHODS

A prospective cohort study was conducted in the surgical wards of Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) over a six-month period. Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (M110652). All study participants provided verbal informed consent. During the hospital admission, participants completed a written questionnaire with the assistance of a research nurse who was fluent in the commonly used languages. Assigning a study number to each questionnaire ensured patient confidentiality. Data collected included demographic information, medical history and details of analgesic use. On discharge, the relevant clinical, radiological, pharmacological, endoscopic and surgical information was collected from the patient's clinical notes in the hospital file.

Study population

The study population was inclusive of all patients older than 12 years, admitted to the surgical wards during the study period. The study sample included patients with signs and symptoms of an acute UGIT bleed, confirmed by oesophagogastroduodenoscopy (OGD). Patients with pathology secondary to portal hypertension, Mallory-Weiss tears, oncological lesions, arteriovenous malformations, and incomplete questionnaires were excluded.

Data capture and analysis

The data from both hospitals were combined and entered into a master Microsoft Excel spreadsheet. Patients were categorised based on their proclivity to use NSAIDs into two groups, 'NSAID' and 'no NSAID' use. Descriptive statistical analysis was performed on the demographic data and medical history. Subgroup analysis was performed for the patients who utilised NSAIDs as to the source of the NSAIDs as OTC or on prescription. SAS 9.3™ was used for statistical analyses. Where

parametric t-Tests could not be used due to unequal variance, non-parametric Wilcoxon tests were used. Categorical data were compared using the Pearson's Chi Squared test.

p -values < 0.05 were considered significant.

UGIT bleed treatment cost calculation

The cost of UGIT bleeds was estimated by aggregating the cost of procedures performed to treat the UGIT bleed, medications, blood products and ward fees for each patient. The cost structure was based on unit costs of procedures, admissions, consultations, medications, blood products and imaging at a university-affiliated private sector hospital (Appendix 1) as the public sector costs were not easily obtainable. Expenditure on resuscitation measures, acute management and laboratory tests as well as the use of disposable materials and equipment initiated in the emergency department and continued in the ward were not included as the costs are assumed as standardised for all patients in these hospitals.

RESULTS

During the study period, 321 patients were admitted for treatment of an UGIT bleed, of which 68 were excluded from analysis as shown in Figure I. Closer examination of the 68 exclusions, showed that there were twelve mortalities, of which five were unable to give consent (three were intubated and ventilated on arrival and two were in a state of confusion). The remaining seven patients all used OTC NSAIDs. All twelve mortalities were excluded from the cost analysis as all required prolonged organ support and multiple interventions that would have skewed the results. A further three patients who could have been included in the 'NSAID use' group were

excluded as the details regarding OTC or prescription NSAID use were not clearly provided.

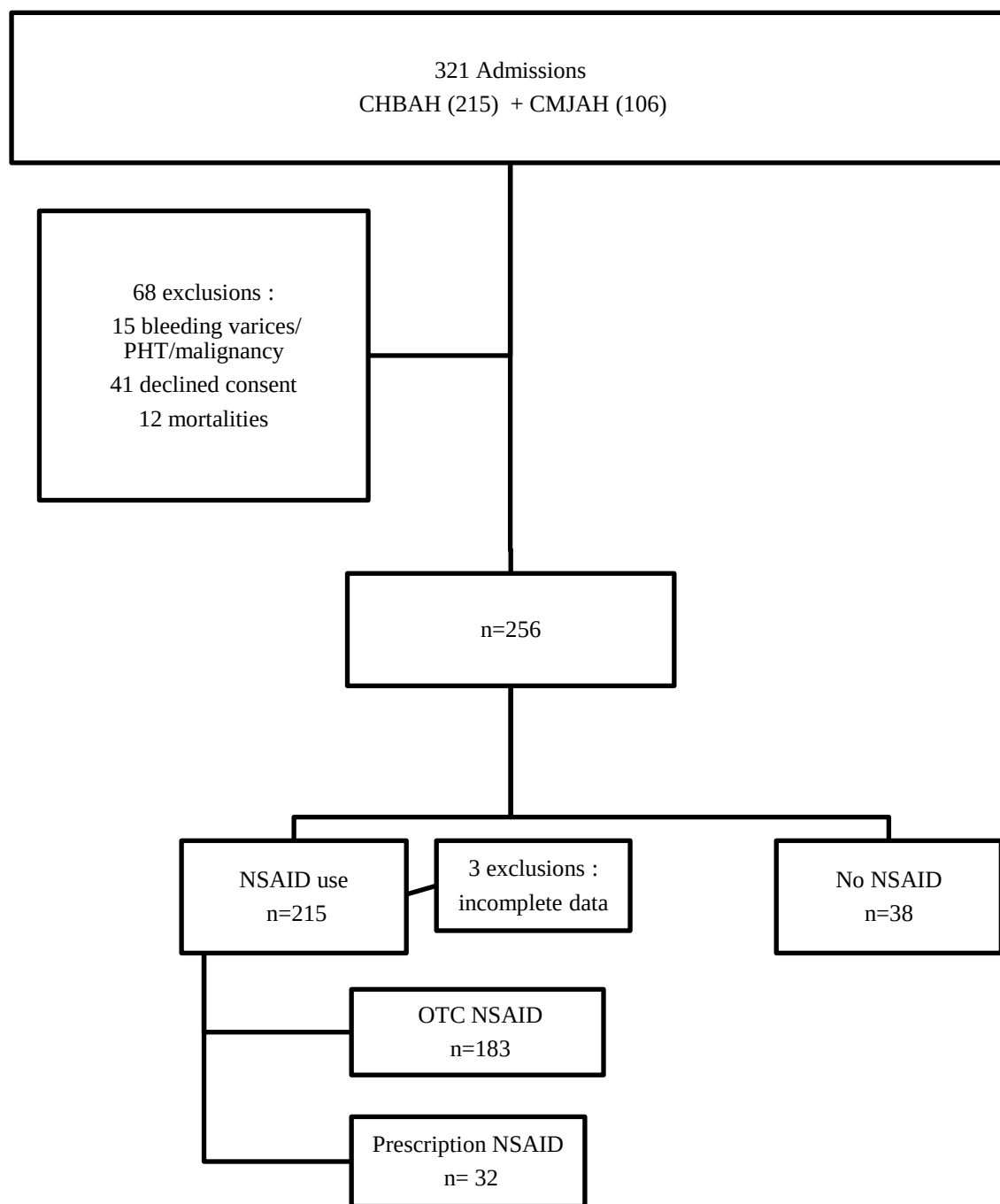


Figure 1: Study flow diagram

CHBAH Chris Hani Baragwanath Academic Hospital; CMJAH Charlotte Maxeke Johannesburg Academic Hospital; PHT portal hypertension; NSAID non-steroidal anti-inflammatory; OTC over the counter

Table I. Demographic characteristics of patients using OTC NSAIDs vs patients using NSAIDs obtained on prescription (n=215)

Values expressed as number (% of n=215)

		OTC NSAID	NSAID on prescription	<i>p</i> -value
Demographics	Average Age in years (range)	50 (14-87)	60 (19-88)	0.005
	Gender			
	Male	101 (47)	14 (6)	
	Female	82 (39)	18 (8)	
	Employment status			
	Employed	59 (27)	5 (2)	
Social habits	Smoker	77 (36)	9 (4)	
	Alcohol	74 (34)	10 (5)	
Co-Morbidities	Hypertension	58(27)	21 (10)	0.0004
	Diabetes	18(8)	7(3)	0.05
	HIV	20(9)	2(1)	
	Asthma	5(2)	1(0)	
	Arthritis	2(1)	3(1)	0.0004
	Peptic ulcer disease	41(19)	13(6)	0.04
	Other	7(3)	3(1)	
Indication for analgesia	Dental pain	6(3)	0	0.001
	Headache	79(37)	4(2)	
	Musculoskeletal pain	62(29)	15(7)	
	Abdominal pain	35(16)	9(4)	
	Other	12(6)	5(2)	

Table I illustrates the demographic and clinical characteristics of the study participants. NSAID use was reported by the majority (85%) of the 256 participants, with no NSAID use reported by only 38 of the participants. Medical co-morbidities that demonstrated significant differences between the groups were hypertension ($p=0.0004$), diabetes ($p=0.05$), arthritis ($p=0.0004$) and peptic ulcer disease ($p=0.04$). Patients were not asked specifically about any chronic medication, other than analgesics, they used.

The most common indication for OTC NSAID use in our population was headaches, musculoskeletal and abdominal pain followed. The majority of the population (% or n) surveyed did not require chronic analgesia on prescription for any of these common ailments.

Smoking and alcohol, in our population were not statistically significant in both groups of patients.

Table II provides details of the analgesic usage patterns and includes data from patients using more than one type of OTC analgesic.

Table II: Incidence of analgesic use by 183 participants

Values expressed as % of n=183 (number)

Analgesic class	% of patients using analgesics
Grand-Pa™ Headache Powder (Acetyl salicylic acid-paracetamol-caffeine combination)	57.4%
Paracetamol	34.4% $p=0.035$
Ibuprofen	8.7% $p=0.02$
Aspirin (acetyl salicylic acid)	32.8%
Other NSAID and/or combination analgesics (Paracetamol/Codeine, Paracetamol/Ibuprofen, Paracetamol/Acetyl salicylic acid, Paracetamol/Ibuprofen/Codeine, Diclofenac and Indomethacin).	32.8% $p=0.004$

It is interesting to note, that in the population served by the public health system, no patient surveyed used a selective COX inhibitor. Patients named other NSAID combinations by the trade name the drug was sold as. MIMS prescribing guide ⁹ was used to confirm the constituents and the pharmacological name of the drug used. No

one obtained Grand-Pa [™] on prescription. P values included in the table compare the use of these medicines OTC and by prescription.

Table III examines the patterns of use of OTC and prescription NSAIDs. The results indicate that patients may take more medication more often than is recommended as indicated by the significant *p*-value (0.0003) comparing the group of patients taking both OTC and prescription NSAIDs three times a day. The population surveyed was very brand-loyal. Only five percent of OTC NSAID users considered cost as a factor when purchasing analgesics, 95% of patients indicated that they preferred to use brands they trusted, that had proven effect in the past and would reliably relieve their symptoms irrespective of cost. (Not statistically significant)

Pertaining to instructions on use, although none of the results between the two groups were statistically significant, a minority (13%) of patients was aware of the side effects of either type of drug. Few patients were given any advice when purchasing/collecting the NSAIDs. Of the patients taking OTC NSAIDs, fifty three percent of patients surveyed (n=215) took OTC NSAIDs with meals compared to 10% of the group taking prescription NSAIDs (n=215). Eight percent of patients using an OTC NSAID concomitantly used an antacid or proton pump inhibitor, compared to two percent of patients using OTC obtained on prescription (Table III).

Table III: Patterns of use of NSAIDS 215 respondents

Values represented as number (%)

		NSAID USE n=215	
		OTC n=183	Prescription n=32
Frequency of use	Daily	84(39)	11(5)
	Twice daily	38(18)	6(3)
	Thrice daily	37(17)	16(7)
	Four times daily	5(2)	1
	>Four times daily	37(17)	3(1)
Influenced by cost		11(5)	0
No. of tablets/dose	0.5	9(4)	7(3)
	1	86(40)	11 (5)
	2	83(38)	14(7)
	3	15(7)	0
	4	7(3)	1
	Other	14(7)	1
Instructions on use	Side Effects	23(11)	4(2)
	Advice	14(7)	5(2)
	Meals	114(53)	22(10)
	Antacid	29(13)	3(1)
	PPI	17(8)	5(2)

Table IV outlines the details of the hospital admission. The relevant clinical information was collected from the hospital file after the patient was discharged. None of the parameters examined were statistically significant when the two groups were compared (Table IV). The findings suggest that the cost to treat upper gastrointestinal bleeds was comparable and was not influenced by the type of NSAID used by the patient. Costs were calculated using the cost structure in Appendix 1, where unit costs were multiplied by the number of days in hospital, invasive and non-invasive procedures and blood products consumed. Data collection did include intravenous medications and radiological investigations. However this data were excluded in the table, as there was no difference in cost between the two groups.

Table IV: Details of the hospital admission, in-hospital treatment and calculation of costs of NSAID vs. Non- NSAID users.

	NSAID users			Non-NSAID users
	TOTAL	OTC NSAID	Prescription OTC	
Number of Participants	215	183	32	38
Age (years) Mean [Range (SD)]	51 [14-88 (18)]	50 [14-87 (17)]	60 [19-88 (21)]	46 [18-84 (20)]
Hospital admission Mean [Range (SD)]				
Length of stay (days)	6.3 [2-54 (5)]	6.23 [2-54 (6)]	6.5 [2-30 (5)]	5.74 [2-16 (5)]
ICU length of stay (days)	0.3 [0-19 (0.3)]	0.29 [0-19 (1.82)]	0.13 [0-2 (0.49)]	0.11 [0-4 (0.65)]

Endoscopy Mean [Range (SD)]				
OGD (n)	1 [0-4 (0.7)]	0.97 [0-4 (0.7)]	1.09 [0-3 (0.69)]	1 [0-2 (0.57)]
Interventional OGD (n)	0.02 [0-1 (0.15)]	0.02 [0-1 (0.15)]	0.03 [0-1 (0.18)]	1 [0-1 (0.23)]
Injection (n)	0.12 [0-1 (0.32)]	0.10 [0-1 (0.3)]	0.22 [0-1 (0.42)]	0
Surgery Mean [Range (SD)]				
Laparotomy (n)	0.11 [0-1 (0.32)]	0.11 [0-1 (0.31)]	0.09 [0-1 (2.9)]	0.08 [0-1 (0.27)]
Relook laparotomy (n)	0.05 [0-7 (0.49)]	0.05 [0-7 (0.53)]	0	0

Blood Products				
Mean [Range (SD)]				
Packed Red Cells (units)	1.96 [0-17 (2.64)]	1.94 [0-15 (0.15)]	1.66 [0-7 (2.06)]	1.61 [0-9 (2.2)]
Fresh frozen plasma (units)	0.39 [0-7(1.13)]	0.39 [0-7 (1.13)]	0.25 [0-4 (0.84)]	0
Platelets (units)	0.05 [0-2 (0.28)]	0.04 [0-2 (0.27)]	0.06 [0-2 (0.35)]	0.03 [0-1 (0.16)]
Subgroup cost	R 9 194 698	R 7 592 260	R 1 602 438	R 1 268 970
TOTAL COST	R 10 463 668			

p values indicate no statistical differences(all >0.05) between the groups(NSAID vs Non-NSAID user) compared. SD: Standard Deviation. ICU: Intensive Care Unit (includes High Care). OGD: Oesophagogastroduodenoscopy, intervention includes any other method to treat visible ulceration or bleeding other than injection of normal saline or adrenaline.

The cost of treatment for all UGIT bleeds during the six-month period was R 10 463 668 (n=253). Patients using NSAIDs (n=215) accounted for 88% (R 9 194 698) of the cost. Of the patients who used NSAID's, 85% (n=183) obtained the NSAIDS as OTC medication and the treatment cost of R 7 592 260, which amounted to 73% of the total expenditure.

The average cost to treat a patient with UGIT complications secondary to OTC vs. Prescription NSAIDs was not statistically significant. (Pearson Chi Square test) Overall due the higher number of patients who used OTC NSAIDs the cost incurred to treat these patients was five fold more than to treat the patients taking prescription only NSAIDs.

DISCUSSION

The South African Essential Medicines List (SAEML) proposes ibuprofen as an alternate analgesic to paracetamol in the first line management of pain.¹⁰ No alternative is suggested for ibuprofen, and consequently the use of NSAIDs is common in South Africa. This study was conducted in two tertiary hospitals in the public health care environment where patterns of OTC NSAID use and their relationship to UGIT bleeds have not previously been characterised.

During the study period, 70% (n=215) of patients who were admitted with UGIT bleeds used NSAID's, 85% (n=183) of whom obtained their NSAIDs without a prescription. The incidence of OTC NSAID use was found to be far greater in the South African setting than in lower socioeconomic groups in first world countries, where 44% of patients admitted for UGIT haemorrhage used OTC NSAIDs.⁴ The implication is that South African consumers, specifically in the lower socioeconomic

groups, appear to obtain OTC NSAIDs easily but are not being provided with adequate information to guide their decision-making.

In the current study the three most significant risk factors for UGIT bleeds requiring hospital admission were advanced age, multiple medical co-morbidities and HIV infection as indicated by *p*-values in Table I.

Age

Advanced age itself has been shown to be an independent risk factor for UGIT bleeding as well as the most widely reported risk factor for UGIT bleed-associated mortality.¹¹ Approximately 40-60% of NSAID consumers are over 60 years of age,¹² and up to 95% of elderly patients taking NSAIDs may obtain their medication OTC.¹³ Of the individuals in the current study older than 60 years of age, 33% (n=72) used NSAIDs of whom 79 % (n=57) obtained them OTC. In the Western world, the proportion of older patients suffering from UGIT bleeds has increased over recent years, mostly due to increased life expectancy and widespread NSAID use.¹¹ South Africa's population older than 60 years of age has increased from 2.8 million (1996) to 4.1 million (2011) with projections of 7 million by 2030. Current socio-economic assessments estimate that 40% of the elderly live in poverty, 38% rely on chronic medication and 28 % have no formal education.¹⁴ In view of the fact that the risk of an UGIT bleed increases from 1.65 per 100 000 in patients <65 years to 5.7 per 100 000 in those >65 years and 12.7 per 100 000 in patients >75 years of age^{15,16} together with social and economic deficiencies the potential cost to SA healthcare is significant.

Co-morbidities

Epidemiological studies have demonstrated non-gastrointestinal comorbidities (hypertension, diabetes and arthritis) as independent risk factors for UGIB.¹⁷ This association was evident in the study participants taking OTC NSAIDs (Table I).

HIV

Pain is a common symptom in people living with HIV and AIDS, occurring in 60% to 98% of patients in South Africa.¹⁸ The South African Essential Medicines List (SA EML) treatment protocol for management of adult HIV and AIDS related pain recommends paracetamol and/or ibuprofen first line treatment. A study conducted at a primary health care facility in the city of Tshwane determined that ibuprofen was prescribed for 44% of patients and aspirin (acetyl salicylic acid), at analgesic doses, for 18%.¹⁹ In addition, 84% of prescriptions contained suboptimal drug dosages and an insufficient quantity of tablets to sustain the patient to the next appointment, consequently more than 25% of the sample population used OTC analgesia.

In a study conducted at an HIV clinic in Houston Texas OTC NSAIDs accounted for 38% of the most commonly used medications.² All of the patients taking NSAID's were prescribed gastro protective agents (GPAs) and the reported adverse drug reactions with concurrent antiretroviral treatment was 16 %, with most of the ADRs classified as type II drug reactions. In our study 22 patients volunteered their HIV status as positive and all of the 22 patients used NSAID's, 20 as OTC NSAIDs and two as prescription NSAIDs. None of these patients took GPAs. GPAs are not listed in the SA Primary Care EDL. Approximately 6.4 million people in South Africa live with HIV,²⁰ consequently, the potential cost of NSAID related UGIT bleeds in this population group is prodigious.

Economics

The cost of NSAID induced gastropathy has been best quantified in the elderly, a population group that exhibits a high baseline rate of gastrointestinal bleeding,²¹ as well as being the highest consumer group of NSAIDs.²² Medical costs to treat the complications of UGIT bleeds in the elderly who use prescribed NSAIDs in the USA have been estimated at over \$4 billion per year, and the annual cost attributed to lost

work productivity and care exclusive of treatment expenditure amount to \$5.65 billion. ²³A limitation of these cohort healthcare cost studies is that OTC medication use is not included as these are paid for by the patient, hence these costs are not captured in clinical billing databases.

In South Africa more than 80% of the population do not have medical insurance, and studies have shown that many patients deem self-funded primary health care visits as expensive as well as inconvenient²⁴. South African consumers have also been shown to perceive generic medicines, obtained at no cost from public healthcare providers, as inferior and of poor quality.²⁵ This places limitations on national medicine policies and may influence consumers to purchase specific, preferred brands of analgesics.

Self-medication is predicted to demonstrate a constant compound annual growth rate of 2% with ibuprofen expected to show amongst the strongest growth.²⁶In 2009 pharmaceutical manufacturers updated and innovated their products to accommodate this expanding group of consumers. Grand-Pa™ Headache powder (acetyl salicylic acid-paracetamol-caffeine) is sold only in Southern Africa. As at 2015, it leads the analgesic market with a 45.6% market share competing with Panado™ (paracetamol) with a brand retail value share of 20.7%, Disprin™ (acetyl salicylic acid) with 17.9% market share and Compral with a 7.1 % market share (Agola 2016) These brands are household names with a historical role in influencing customer choice, are widely available in both formal and informal retailers and are trusted and supported by strong marketing campaigns.

Continental Outdoor Media is an advertising company that published their 2013 marketing strategy for Grand-Pa™ in Shoshanguve, an informal settlement 25km north of Pretoria. According to data from Nielsen Research, Grand-Pa™ is a market leader in the analgesics market contributing 39% to the total category sales value. Its

main competitors are Disprin™ (Reckitt Benckiser), Anadin™ (Pfizer), Panado™ and Compral™ (both Tiger Brands) – these collectively contributing 54% to the total category sales value.

The impact of an outdoor advertising campaign demonstrated strong impact on sales of Grandpa powders that despite introduction of the new tablet formulation (not available at the time of the study), was the driver of overall brand growth. The main volume gain was captured from Panado and a total sales increment of 3.5 % was gained with one well-placed billboard.

These well-marketed brands are household names with a historical role in influencing customer choice, and are trusted and therefore widely available in both formal and informal retail settings as well as being supported by strong marketing campaigns.²⁶

NSAID use in the South African public healthcare system does not mirror that of the private healthcare sector³. Selective cyclooxygenase-2 inhibitors are a group of NSAIDs, which have a significantly lower incidence of UGIT side effects. However, none of the surveyed population were prescribed these drugs (Table II). Proton pump inhibitors were used by 8% and 2% in both the OTC and prescription NSAID use groups. Both drug classes are not included in the SA Primary Care EML.

Study Limitations

Economic assessments to determine overall cost include evaluation of direct, indirect (productivity losses) and intangible (impaired quality of life) costs. Our study considered direct monetary costs hence it underestimates the actual cost to individual as well as to society. We excluded the 12 patients that died during their admission, seven of whom were OTC NSAID users. Of the remaining five, we were unable to determine the extent of NSAID usage. This omission may further have underestimated the cost of NSAID related complications.

NSAID use (including low dose acetyl salicylic acid) and *H.pylori* infection are among the most common independent risk factors for UGIB.²⁷At the time of the study, CLO (*Campylobacter*-like organism) tests were not available during endoscopy hence the synergistic and additive effect of *H.pylori* infection with NSAIDs could not be assessed.

The study questionnaire specific to chronic drug use required a yes or no response from the participant but did not extend to the type of medications used. This omission does not allow the data to be interpreted including the potential UGIT effects of these specific medications and their varying formulations. A further limitation of the questionnaire is that the questions pertaining to the patterns of use of analgesics did not clearly distinguish frequency and duration of use. As a result analysis of the duration of use could not accurately be performed.

The two hospitals involved in the study have differing age criteria for admission to the adult surgical wards.

At Chris Hani Baragwanath Hospital, any patient over the age of 10 is considered an adult. At Charlotte Maxeke Academic hospital any patient over the age of 16 is considered an adult. As a result there may have been patients over the age of 12 in both hospitals that may have not been included in the study as they may have been admitted to the paediatric surgical service.

Lastly, this study was conducted in two of Gauteng's tertiary public hospitals. The population served by these hospitals may not fully represent the spectrum of NSAID use from all parts of the country. It is not possible to know, from our study, the proportion of the population who use NSAIDs.

CONCLUSION

NSAID use is common in South Africa and the majority of patients presenting with upper gastrointestinal tract adverse effects were taking NSAIDs obtained OTC. These complications are potentially fatal and potentially preventable. Patients are inadequately educated on the dangerous side effects and may not always take the medication correctly. Not many patients who experience upper GI adverse effects are taking gastro protective agents.

The cost to treat patients with upper GIT adverse events for the study period of six months was just in excess of R10 000 000. This cost to public health in a setting of resource constraint is substantial.

REFERENCES

1. Bidaut-Russell M, Gabriel SE. Adverse gastrointestinal effects of NSAIDs: consequences and costs. *Best Pract Res Clin Gastroenterol* 2001 Oct;15(5):739–753. [<http://dx.doi.org/10.1053/bega.2001.0232>][PMID: 11566038]
2. Ajuoga E, Sansgiry SS, Ngo C, Yeh RF. Use/misuse of over-the-counter medications and associated adverse drug events among HIV-infected patients. *Res Social Adm Pharm.*2008 Sep;4(3):292–301. [<http://dx.doi.org/10.1016/j.sapharm.2007.08.001>][PMID: 18794039]
3. Dyssel N. The analgesic market in South Africa – A critical review of contributing growth factors over the past four years.[Dissertation] University of Stellenbosch; 2012.

4. Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. *Arch Intern Med*.1994 Jan 10;154(1):42–46.[<http://dx.doi.org/10.1001/archinte.154.1.42>] [PMID: 8267488]
5. Straus WL, Ofman JJ. Gastrointestinal toxicity associated with anti-inflammatory drugs. *Gastroenterol Clin North Am*. 2001 Dec;30(4):895–920.
[[http://dx.doi.org/10.1016/s0889-8553\(05\)70219-3](http://dx.doi.org/10.1016/s0889-8553(05)70219-3)] [PMID: 11764534]
6. Rodriguez LAG, Tolosa LB. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. *Gastroenterology*. 2007;132:498-506
7. Straube S, Tramer MR, Moore RA, Derry S and McQuay HJ. Mortality with upper gastrointestinal bleeding and perforation: effects of time and NSAID use. *BMC Gastroenterology*.2009;9:41.[<http://dx.doi:10.1186/1471-230X-9-41>]
8. Bornman MS. Organ-Specific warnings; Internal Analgesia, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph. Final rule. *Federal Register*.2009;74(81): 19385 – 19409.
[Online] www.gpo.gov/fdsys/pkg/FR-2009-04-29/pdf/E9-9684.pdf
[Accessed on 19 January 2015]
[PMID: 19507324]
9. MIMS (Monthly index of Medical Specialities) Desk reference. Volume 51. July 2016.

10. Standard Treatment Guidelines and Essential Medicines List for South Africa. Fifth edition. Pretoria. The National Department of Health 2014. Chapter 12. [Online] www.kznhealth.gov.za/pharmacy/edlphc2014a.pdf [Accessed 17 October 2016]

11. Rahme E, Joseph L, Kong SX, et al. Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients. *Br J Clin Pharmacol*. 2001 Aug;52(2):185–92. [<http://dx.doi.org/10.1046/j.1365-2125.2001.00348>][PMID: 11488776]

12. Gurwitz JH, Avorn J. The Ambiguous Relation between Aging and Adverse Drug Reactions. *Ann Intern Med* 1991 Jun 1;114(11):956. [<http://dx.doi.org/10.7326/0003-4819-114-11-956>][PMID: 2024864]

13. Cebollero-Santamaria F, Smith J, Gioe S, Frank T, et al. Selective outpatient management of upper gastrointestinal bleeding in the elderly. *Am J Gastroenterol*. 1999 May;94(5):1242–7. [<http://dx.doi.org/10.1111/j.1572-0241.1999.01073>][PMID: 10235201]

14. Lehohla P. Census 2011 – Profile of older persons in South Africa. Statistics South Africa. Pretoria 2014. [Online] Report No.03-01-60. Available from: www.statssa.gov.za [Accessed 19 January 2015]

15. Hansen JM, Hallas J, Lauritsen JM, et al. Non-Steroidal Anti-Inflammatory Drugs and Ulcer Complications: a Risk Factor Analysis for Clinical Decision-Making. *Scand J Gastroenterol*. 1996 Jan;31(2):126–30. [<http://dx.doi.org/10.3109/00365529609031975>][PMID: 8658033]

16. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for Serious Gastrointestinal Complications Related to Use of Nonsteroidal Anti-inflammatory Drugs: A meta-analysis. *Ann Intern Med*. 1991 Nov 15;115(10):787-796.[<http://dx.doi.org/10.7326/0003-4819-115-10-787>] [PMID: 1834002]
17. Crooks CJ, West J, Card TR. Comorbidities Affect Risk of Nonvariceal Upper Gastrointestinal Bleeding. *Gastroenterol*. 2013 Jun;144(7):1384–1393. [<http://dx.doi.org/10.1053/j.gastro.2013.02.040>] [PMID: 23470619]
18. Norval DA. Symptoms and sites of pain experienced by AIDS patients. *S Afr Med J*. 2004; 94(6): 450–454. [<http://dx.doi.org/10.7196/samj.2620>] [PMID: 15250459]
19. Maree JE, Dreyer Wright SC, Makua MR. The Management of HIV- and AIDS-Related Pain in a Primary Health Clinic in Tshwane, South Africa. *Pain Manag Nurs*. 2013 Jun;14(2):94–101. [<http://dx.doi.org/10.1016/j.pmn.2010.10.037>] [PMID:23688363]
20. Shisana O, Rehle T, Simbayi LC, et al. (2014) South African National HIV Prevalence, Incidence and Behaviour Survey, 2012 Cape Town, HSRC Press.
21. Smalley WE, Ray WA, Daugherty JR, et al. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalisations for peptic ulcer disease in elderly persons. *Am J Epidemiol*. 1995.141; 539-545. [<http://dx.doi.org/10.1007/BF02599040>] [PMID: 7900721]
22. Ahmed A, Stanley AJ. Acute Upper Gastrointestinal Bleeding in the Elderly. *Drugs Aging*. 2012 Oct 12;29(12):933–40. [<http://dx.doi.org/10.1007/s40266-012-0020-5>] [PMID: 23192436]

23. Kendall BJ, Peura DA. NSAID associated gastrointestinal damage and the elderly. *Pract Gastroenterol*.1993;17: 13-20.
24. Mayosi BM, Benatar SR. Health and Health Care in South Africa — 20 Years after Mandela. *N Engl J Med*; 2014 Oct 2;371(14):1344–53.
[<http://dx.doi.org/10.1056/nejmsr1405012>][PMID:25265493]
25. Patel A, Gauld R, Norris P. Rades. Quality of generic medicines in South Africa. Perceptions versus Reality – A qualitative study. *BMC Health services research*.2012;12:297
26. Analgesics in South Africa Market Research Report
<http://www.euromonitor.com/analgesics-in-south-africa/report>
[Accessed 19 January 2015]
27. Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*. 2002 Jan;359(9300):14–22. [[http://dx.doi.org/10.1016/s0140-6736\(02\)07273-2](http://dx.doi.org/10.1016/s0140-6736(02)07273-2)]
[PMID:11809181]

Word count: 4059

APPENDIX 1

Treatment, investigation and procedural costs obtained from a university- affiliated hospital. Estimated costs for 2013.

Currency: South African Rand (R)

Hospital Cost per day	Initial consult with surgeon	R 3405
	Subsequent admission in a general ward	R 2905
	Intensive care unit admission - initial	R 13270
	Subsequent days in ICU	R 11270
	Ward admission cost	R 6409
Surgical Interventions	Gastroscopy	R 3000
	Endoscopic injection with adrenaline	R 100
	Biopsy of lesion	R 100
	Sclerotherapy	R 3000
	Laparotomy – theatre time charged at 138.20/minute	R 18600
	Relook laparotomy – shorter duration of surgery assumed	R 9000
Blood products	Packed red cells	R 5000
	Platelets (mega unit)	R 8000
	Fresh Frozen Plasma	R4800
Medication	Pantoprazole (intravenous)	R 600
	Chest radiograph	R 600
Radiology	Abdominal radiograph	R 600
	Computerized tomogram	R 2000
	Abdominal ultrasound	R 800

APPENDIX 1.

Cost Structure Treatment, [investigation](#) and procedural costs obtained from a university- affiliated hospital.

Estimated costs for 2013.

Currency: South African Rand (R)

Hospital Cost per day	Initial consult with surgeon	R 3405
	Subsequent admission in a general ward	R 2905
	Intensive care unit admission - initial	R 13270
	Subsequent days in ICU	R 11270
	Ward admission cost	R 6409
Surgical Interventions	Gastroscopy	R 3000
	Endoscopic injection with adrenaline	R 100
	Biopsy of lesion	R 100
	Sclerotherapy	R 3000
	Laparotomy – theatre time charged at 138.20/minute	R 18600
	Relook laparotomy – shorter duration of surgery assumed	R 9000
Blood products	Packed red cells	R 5000
	Platelets (mega unit)	R 8000
	Fresh Frozen Plasma	R4800
Medication	Pantoprazole (intravenous)	R 600
	Chest radiograph	R 600
Radiology	Abdominal radiograph	R 600
	Computerized tomogram	R 2000
	Abdominal ultrasound	R 800

CHAPTER 4. APPENDICES

APPENDIX 1. POSTER



Over the Counter NSAIDs should be banned!

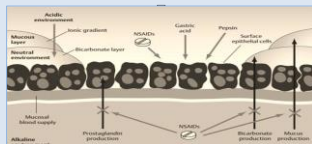
A retrospective cost of illness study in a Johannesburg public hospital.

T Govender, M Brand, P A Maraj Department of Surgery, University of the Witwatersrand

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, cheap and effective analgesics. They work by non-selectively inhibiting prostaglandin synthase (cyclo-oxygenase) types 1 & 2.

These drugs alter normal gastric defence mechanisms locally and systemically (Fig. 1) and may cause serious adverse gastrointestinal effects.



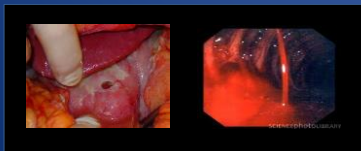
In April 2009, the United States Food and Drug Administration issued a ruling that made it compulsory for manufacturers to list the gastrointestinal and cardiac side-effects of NSAIDs on all NSAID packaging.

In South Africa, NSAIDs are freely available over the counter.

Hypothesis

OTC NSAID use results in serious adverse upper gastrointestinal effects.

There is a major financial burden incurred by public health systems in managing these conditions.



Methods

A retrospective 2010 study at the Charlotte Maxeke Johannesburg Academic Hospital.

We audited hospital records of patients admitted to the general surgical wards who

- Presented with upper gastrointestinal complaints (epigastric pain, haematemesis, melaena)
- Underwent esophagogastroduodenoscopy (diagnostic and/or interventional)
- Underwent laparotomy (for severe bleeding ulcer, Graham-Steele mentopexy, partial gastrectomy)

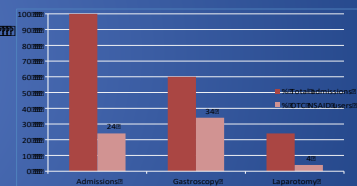
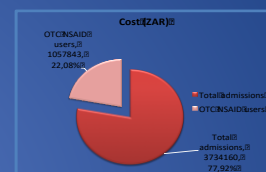
The current cost structure of the Wits Donald Gordon Medical Centre (a University affiliated hospital) was used to calculate the direct medical costs of these admissions (Table 1).

Resources/Procedure	Unit Cost (ZAR)
A. Admission (per day)	
General Surgical Ward	2405
High Care Unit	5929
Intensive Care Unit	14000
B. Endoscopy	
Diagnostic	5500
Interventional	6100
C. Surgery	
Laparotomy (60 min)	9300
D. Radiology	
Chest X-Ray	600
Abdominal X-Ray	600
E. Blood Products	
Packed Red Cells	5000
Platelets	8000
Fresh frozen plasma	4800
F. Consultation Fees	
General Surgeon (initial)	1000
General Surgeon (subsequent)	500
Intensivist (initial)	3200
Intensivist (subsequent)	1200
G. Intravenous Infusion	
Pantoprazole	600

Results

In 2010, 170 patients were admitted with upper GIT complaints.

41 patients used NSAIDs obtained over the counter. Using Table 1, the total direct medical cost calculated was ZAR 1748748.



Conclusions

- OTC NSAID users constituted 24% of patients admitted with upper GIT complaints and incurred 22% of the total direct medical cost.
- This cost is substantial and could possibly be reduced by regulating the OTC sale of NSAIDs.

CHALLENGES

Incomplete and inconsistently recorded data.
Difficulty accessing archived microfilm.
Way Forward...
Prospective categorical data collection in 2011 in 2 provincial Gauteng Hospitals.

References

- United States Food and Drug Administration, (April 28, 2009) Electronic References. Retrieved 03 January 2011 from www.fda.gov

APPENDIX 3. ETHICS APPROVAL

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Theshni Govender

CLEARANCE CERTIFICATE

M110652

PROJECT

Adverse Gastrointestinal Effects of Over the Counter
NSAIDs: a Cost Study in Two Gauteng Public

Hospitals

INVESTIGATORS

Dr Theshni Govender .

DEPARTMENT

Department of Sugery

DATE CONSIDERED

24/06/2011

DECISION OF THE COMMITTEE*

Approved unconditionally

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

DATE 05/08/2011

CHAIRPERSON
(Professor PE Cléaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Martin Brand

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 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 4. RESEARCH PROTOCOL

Cover Page

PROTOCOL

Adverse gastrointestinal effects of over the counter NSAIDs: A cost study in two Gauteng public hospitals.

Dr Theshni Govender
Student Number 9802080G
General Surgery

Supervisor: Dr Martin Brand

Literature Review

“This product contains an NSAID, which may cause severe stomach bleeding.”

On the 24 April 2009, The United States Food and Drug Administration issued a ruling requiring all non-steroidal anti-inflammatory drug (NSAID) manufacturers to list comprehensive warnings on all NSAID packaging effective April 29, 2010.¹ The word ‘severe’ has been accurately and appropriately included in the warning as NSAID induced bleeding is potentially fatal.¹

NSAIDs are among the most commonly used analgesics worldwide. They are available in a variety of formulations of over the counter (OTC) and prescription preparations. They are effective analgesics, anti-pyretics, anti-thrombotics and anti-inflammatories.

The use of OTC NSAIDs has been estimated to be seven-fold greater than that of prescribed NSAIDs³ and shown to increase with age with approximately 40- 60% of NSAID consumers are over 60 years of age.⁴ The Foundation states that , globally, approximately 35 000 metric tons are produced and consumed annually, enough to manufacture more than 100 billion 325mg aspirin tablets.⁵

The World Health Organization (WHO) analgesic ladder describes pain in mild, moderate and severe degrees.¹⁰ Acute, mildly painful conditions that are amenable to self-medication with an over the counter NSAID preparation, include headaches, toothache, dysmenorrhoea, minor musculoskeletal injuries and pain associated with upper respiratory tract infections.

Despite the wide range of OTC NSAID preparations marketed for the treatment of these conditions, the constituent active, non-steroidal components are primarily acetyl salicylic acid, ibuprofen, diclofenac and indomethacin. These four NSAIDs are classified as essential drugs by the South African Department of Health (Essential

drugs are those medications that are critically required for either the prevention or management of the common and important illnesses in the country) First line pain management, as outlined by the SA Essential Drug List treatment protocol is paracetamol, followed by ibuprofen. No alternative is suggested for ibuprofen². In contrast the WHO only classifies (acetyl salicylic acid) as an essential drug and ibuprofen in the WHO therapeutic group category (where various other drugs may serve as alternatives).

NSAIDs relieve pain by inhibiting prostaglandin synthesis via prostaglandin cyclooxygenase (COX), which exists in two forms. The COX-1 enzyme is involved in maintaining normal, protective gastric function and COX-2 is up regulated in areas of inflammation. Individual compounds have varying affinities for COX-1 and COX-2. OTC NSAIDs are non-selective and inhibit both forms of COX. They are toxic to the gastric mucosa, causing injury by local irritative as well as systemic effects.

NSAIDs alter normal gastric defence mechanisms by:

- Inhibition of prostaglandin synthesis, they decrease the secretion of mucus and bicarbonate
- Inhibiting regulation of acid secretion and mucosal proliferation
- Decreasing local blood flow
- Compromising platelet and coagulation mechanisms⁶

Gastro-intestinal complications related to NSAID therapy are the most prevalent category of adverse drug reactions. ⁷ It requires only a single dose of a non-selective NSAID to effect some degree of gastric erosion in almost all patients.⁸

These complications can broadly be classified into 3 groups:

- The 'nuisance' symptoms: dyspepsia, heartburn, vomiting, nausea and epigastric pain
- More severe adverse effects: mucosal lesions visible endoscopically or radiologically
- Serious complications requiring hospitalisation (perforation, haemorrhage)⁹

These complications can occur in two time periods, acutely while taking the medication, or more commonly up to two weeks after completing a course.

In South Africa, NSAID preparations are readily available in pharmacies, grocery stores and a myriad of other formal and informal outlets. The sale, advertising and packaging of these medications is not regulated.

Hypothesis

The proportion of patients admitted with upper gastro-intestinal tract (UGIT) symptoms who use OTC NSAIDs is considerable.

The financial cost incurred in treating these patients is a substantial percentage of the total cost spent on patients with UGIT symptoms.

Study objectives

I will quantify the direct cost incurred by two provincial hospitals in the diagnosis and treatment of all patients who present with upper GIT complaints and calculate the proportion of this cost that is spent on patients who were taking NSAIDs obtained OTC.

Methods

The study has two phases:

1. A retrospective study - to assess the incidence of upper gastrointestinal complications related to OTC NSAID use.
2. A prospective observational cost of healthcare study – to assess patterns of NSAID use and their complications

The first phase of the study has been completed and necessitated the second phase as a result of inadequate history taking.

1. Retrospective observational study

Data was collected from 01 January 2010 to 31 December 2010 at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) – Adult General Surgery admission wards, 394 and 396.

(Results of this study: Addendum 1)

Inclusion criteria:

Consecutive patients who were admitted with an UGIT complaint, including epigastric pain, haematemesis and malaena who were self-administering a non-selective NSAID-containing preparation obtained OTC that underwent oesophagogastroduodenoscopy (diagnostic and or interventional) and or a laparotomy (oversewing of a bleeding ulcer; Graham-Steele omentopexy; partial gastrectomy).

Exclusion criteria:

- Patients presenting with upper gastrointestinal symptoms as a consequence of portal hypertension, arteriovenous malformations or Mallory-Weiss tears as diagnosed by oesophagogastroduodenoscopy
- Patients who were not admitted

Data was be obtained from:

- i) The admission registers in ward 394 and 396
- ii) Oesophagogastroduodenoscopy records
- iii) The emergency theatre register
- iv) Patient files archived on microfiche in the medical records department.

Parameters that were recorded from patient files (medical records), endoscopy records and operative notes, was anonymised and recorded on a separate password protected data sheet: see Addendum 2

1.2. **Prospective observational study** from 01 June 2010 to 31 May 2012 at the Charlotte Maxeke Johannesburg Academic Hospital and at the Chris Hani Baragwanath Hospital.

Inclusion, exclusion criteria and patient parameters as described previously.

We will record the hospital number and demographic data daily from admitted patients fulfilling the inclusion criteria.

These patients will be requested to complete an anonymous questionnaire with assistance from the staff at the CMJAH /CHB Department of Surgery – Research division. This questionnaire will provide us with a detailed history, particularly pertaining to patterns of NSAID use and address the deficiency of the retrospective study.

(See Addendum 3 for information sheet and questionnaire)

To calculate the total direct healthcare cost of these admissions, we will use the current (as of 01.01.2011) cost structure utilised by the Wits Donald Gordon Medical Centre, a university affiliated hospital. (See Addendum 4)

Direct cost of resources consumed per patient will be calculated by multiplying volumes by the cost per unit.

The additional cost of personnel other than medical doctors, disposable materials and equipment are not incorporated. Acute management and resuscitation measures instituted in the emergency department and emergency transport to the hospital by ambulance will not be included.

Procedures performed as a direct consequence of complications from the upper gastrointestinal injury or hospitalisation – e.g. Relook laparotomy, treatment of cardiac events will be included.

Data analysis

Direct healthcare cost per patient will be calculated, the sum of which provides the total annual direct medical cost.

Data will be recorded in Microsoft Excel™ and numbers, or mean±std for variables would be recorded in tables and graphs.

Patients will be grouped by NSAID use and a cost comparison between patients who used OTC NSAIDs and those who did not would be determined using a t-test or an appropriate non-parametric test (Mann-Whitney).

Ethics

Approval to conduct both phases of the study will be obtained from the University of the Witwatersrand HREC Committee.

Budget/Funding

None required

Limitations

Personnel to check daily admissions in the surgical wards, identify patients who may be included and conduct the survey/ assist in completion of questionnaire.

Patients with UGIT pathology may be admitted to medical gastroenterology wards and later referred to surgical wards, not necessarily on the same admission. We will have to record their data retrospectively.

Language barrier in completing the questionnaire.

The hospitals involved do not have a computerised record keeping system. There is no database from which to access past patient records (including pharmacy records).

Microfiche records may not always be archived in chronological order, the capturing process may render certain pages illegible, the hospital record numbers may be duplicated, medication records from other clinics (e.g. rheumatology) may be filed and captured separately, patient information may be missing.

Outcomes and benefits

This study will enable us to examine the healthcare expenses incurred by treating a potentially preventable and serious complication of OTC NSAID use in the South African context.

It may highlight the changing perceptions of NSAIDs as 'safe' medicines and enable policy makers in hospitals to motivate for changes in pharmacological classification as a cost cutting measure.

We may potentially influence South African medicine regulatory boards to re-examine the unregulated sale, advertising and packaging of these medications.

References

1. FDA Requires Additional Labelling for Over-the-Counter Pain Relievers and Fever Reducers to Help Consumers Use Products Safely (News Release)
April 28, 2009 <http://edocket.access.gpo.gov/2009/pdf/E9-9684.pdf>
(Accessed on 27 February 2011.)
2. Whittaker C. SA Pharmacist's Assistant (Summer 2009) 8-12

3. Standard Treatment Guidelines and Essential Drug List of South Africa, Primary Health Care, Department of Health 2008
www.doh.gov.za/docs/factsheets/index.html as accessed on 02 March 2011
4. Wilcox CM, Shalek KA & Cotsonis G. Striking prevalence of over-the-counter nonsteroidal ant-inflammatory drug use in patients with upper gastrointestinal haemorrhage. Archives of internal Medicine 1994; **154**: 42-46
5. Gurwitz JH & Avorn J. The ambiguous relation between aging and adverse drug reactions. Annals of Internal Medicine 1991; **114**: 956-966
www.aspirin-foundation.com (accessed on 25 February 2011.)
6. Russell R & Gabriel SE. Adverse gastrointestinal effects of NSAIDs: consequences and costs. Best Practice & Research Clinical Gastroenterology 2001; **15**: 739-753
7. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol Suppl. 1999 Apr; **56**:18-24.
8. Laine L. The gastrointestinal effects of nonselective NSAIDs and COX-2-selective inhibitors. Semin Arthritis Rheum 2002; **32** :25–32
9. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. American Journal of Medicine 1998; **105**:31s-38s
10. [World Health Organisation \(1996\) Cancer Pain Relief 2nd Edn. \(World Health Organisation, Geneva, Switzerland\)](#)

Addendum 1 Retrospective audit results

RESULTS OF THE RETROSPECTIVE STUDY

01/01/2010 – 31/12/2010

Charlotte Maxeke Johannesburg Academic Hospital

In 2010, 170 patients were admitted to the general surgical wards with UGIT complaints.

We confirmed (from recorded history alone) that 41 patients used OTC NSAIDs.

Using the cost structure in Addendum 2

The total cost of healthcare for all patients with upper GIT symptoms was R 3734160.

Patients who used OTC NSAIDs cost R 1057843 (28.3%)

Addendum 2: Clinical information recorded from patient files

Patient record number

Patient demographic data

Ward to which patient was admitted.

Number of days hospitalised in general ward/high care unit/intensive care unit.

History of: smoking; alcohol use; previously diagnosed upper GI condition; concomitant use of steroids/thrombolytic/proton pump inhibitors/H₂ receptor antagonists; hypertension; cardiac disease; medical conditions for which NSAID therapy is prescribed; admission and duration in high care/intensive care unit; endoscopy and findings; surgery and operative findings; quantify blood products (number of units transfused) and pharmacotherapy (intravenous and or oral proton pump inhibitors) during admission and on discharge; details of OTC NSAID use (frequency, type, indication, administration, use of antacids)

Investigations and results:

- Laboratory tests
- Radiography
- Endoscopy (diagnostic and interventional)

Medical management:

- Intravenous medication

- Blood and blood products
- Details of high care/intensive care treatment

Surgical management

- Operative procedures

Outcome:

- Discharge
- Follow-up
- Record morbidities and mortalities

Addendum 3: Questionnaire based survey

Over the counter Non-steroidal Anti-inflammatory drugs should be banned!

Good day. My name is Dr Theshni Govender and I am a registrar in the Department of Surgery at this hospital. I am trying to find out how much people know about commonly used painkillers. I would be most grateful if you could spend a few minutes of your time completing this questionnaire.

The information is completely anonymous and will be used to improve public health care and awareness.

The painkillers we are studying are from a group of medicines called NSAIDs or Non-steroidal anti-inflammatories. These include aspirin(acetyl salicylic acid), Disprin™, Grandpa™, Brufen™, Nurofen™, Voltaren™, Indocid™ and so on.

Please do not feel under any obligation to complete this survey and note that if you prefer not to complete it, your care and treatment will not be affected in any way.

How old are you? _____

What is your gender? M F

What is your occupation? _____

What is the highest educational level you have attained?

No school Primary School High school Post matric

Are you taking any painkillers at present? Yes No

If Yes, which ones? _____

Why do you need to take painkillers? _____

How many tablets/capsules/sachets do you take at a time? _____

How often do you need to take them? _____

Once daily Twice daily Thrice Daily More often

Have you experienced any side effects from painkillers?

Do you get your painkillers on prescription (from a doctor)? Yes No

Do you buy your painkillers over the counter (in shops/pharmacy) ? Yes No

Does the price of the different medicines influence which one you buy?

Yes No

If yes, which medicines do you choose? _____

Do you know what the side effects of these types of painkillers are?

Yes No

If yes, what are they? _____

Have you ever been given any advice about how to reduce side effects from painkillers? Yes No

Does it make a difference if you take the painkillers on an empty stomach as compared with taking them with food?

Yes

No

Do you need to take medicines against stomach acid when you use the painkillers?
(medicines like Rennies™, Amphogel™, Gaviscon™, Zantac™, Losec™)

Yes, which one _____

No

Addendum 4: Cost structure

Costs at WDGMC as at 01/01/11 (Annual inflation across the board) in ZAR

Doctors fee varies with individual practitioners.

Surgeons consult - initial R1000

- Subsequent R500

Theatre time charged at R155/minute

Anaesthetist fees: for G-scope under sedation R1000

for G-scope under GA R2500

Hospital fee for gastroscopy: R2500 (with banding add R600)

Adrenaline injection: cost price of adrenaline/other drugs

Surgeon fee for G-scope: R2000

Intensivist initial consult: R3200

subsequent consults : R1200

Day case: < 24 hours R1536

Overnight stay (fee per day): R2405

High care/ day: R5929

ICU/ day: R10070

Pantoloc infusion: cost price of Pantoloc + consumables (Approx R 600)

Blood transfusion: R2500 (day case)

1 unit Packed red cells: R5000

1 unit Fresh frozen plasma: R4800

1 unit platelets: R 8000

Add R600 for emergency blood

Chest and abdominal radiographs: R600 each

Ultrasonography: R800

APPENDIX 5: Turn It In Report

TheshniGovenderMMedSurg.docx			
ORIGINALITY REPORT			
% 34	% 30	% 18	% 23
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS
PRIMARY SOURCES			
1	www.journals.co.za Internet Source	% 12	
2	www.ncbi.nlm.nih.gov Internet Source	% 2	
3	Submitted to University of Witwatersrand Student Paper	% 1	
4	ir.dut.ac.za Internet Source	% 1	
5	Bidaut-Russell, M.. "Adverse gastrointestinal effects of NSAIDs: consequences and costs", Best Practice & Research Clinical Gastroenterology, 200110 Publication	% 1	
6	wiredspace.wits.ac.za Internet Source	% 1	
7	issuu.com Internet Source	% 1	
8	www.samj.org.za Internet Source	<% 1	
9	Submitted to Tshwane University of		

	Technology Student Paper	<% 1
10	mobile.wiredspace.wits.ac.za Internet Source	<% 1
11	Submitted to University of Maryland, University College Student Paper	<% 1
12	bjgp.org Internet Source	<% 1
13	www.rroij.com Internet Source	<% 1
14	Kay Brune. "Aspirin and acetaminophen: Should they be available over the counter?", Current Rheumatology Reports, 02/2009 Publication	<% 1
15	www.ym.edu.tw Internet Source	<% 1
16	Angelo Zullo. "Bleeding Peptic Ulcer in the Elderly", Drugs & Aging, 2007 Publication	<% 1
17	Submitted to University of Johannesburg Student Paper	<% 1
18	Outhoff, K, JM Dippenaar, M Nell, M Royds, and OBW Greeff. "A randomised clinical trial comparing the analgesic and anxiolytic efficacy and tolerability of Stilpane® and Tramacet® after third molar extraction",	<% 1

Southern African Journal of Anaesthesia and Analgesia, 2015.

Publication

19	Submitted to University of KwaZulu-Natal Student Paper	<% 1
20	www.continentaloutdoor.com Internet Source	<% 1
21	Bennin, Fiona, and Hanna-Andrea Rother. "“But it's just paracetamol”: Caregivers’ ability to administer over-the-counter painkillers to children with the information provided", Patient Education and Counseling, 2015. Publication	<% 1
22	www.mccza.com Internet Source	<% 1
23	www.sapajournal.co.za Internet Source	<% 1
24	codemisused.org Internet Source	<% 1
25	Giorgio Talamini. "Risk Factors of Peptic Ulcer in 4943 Inpatients", Journal of Clinical Gastroenterology, 04/2008 Publication	<% 1
26	Submitted to National University of Singapore Student Paper	<% 1
27	G. M. Peterson. "Improving drug use in	

	rheumatic disorders", Journal of Clinical Pharmacy and Therapeutics, 08/1996 Publication	<% 1
28	Morgan, Helen. "RECOGNISING METASTATIC SPINAL CORD COMPRESSION AND TREATMENT", End of Life Care Journal/17541069, 20091101 Publication	<% 1
29	www.gss.it Internet Source	<% 1
30	www.rwjf.org Internet Source	<% 1
31	www.rxfacts.org Internet Source	<% 1
32	Rolita, Lydia, and Michael Freedman. "Over-The-Counter Medication Use in Older Adults", Journal of Gerontological Nursing, 2008. Publication	<% 1
33	Submitted to University of Iowa Student Paper	<% 1
34	www.herbalgram.org Internet Source	<% 1
35	link.springer.com Internet Source	<% 1
36	rbmfc.org.br Internet Source	<% 1

www.bcbsks.com

37	Internet Source	<% 1
38	Submitted to University of Birmingham Student Paper	<% 1
39	Submitted to University of Delaware Student Paper	<% 1
40	Naidoo, V. G.. "SAGES 2015 Congress Report", South African Gastroenterology Review, 2015. Publication	<% 1
41	www.ed.bmc.org Internet Source	<% 1
42	N/A. "NSAID-related GI disorders costly in Canada's elderly", Inpharma Weekly, 10/2001 Publication	<% 1
43	acadgov.msu.edu Internet Source	<% 1
44	www.gsb.uct.ac.za Internet Source	<% 1
45	www.otago.ac.nz Internet Source	<% 1
46	www.medspecpublishing.co.za Internet Source	<% 1
47	Submitted to China Medical University, Taiwan Student Paper	<% 1

48	cks.library.nhs.uk Internet Source	<% 1
49	Fibuch, Eugene, and Laura Textor. "NSAIDs in the management of acute pain", Handbook of Acute Pain Management, 2010. Publication	<% 1
50	www.chinayiyao.com.cn Internet Source	<% 1
51	Joseph V. Pergolizzi. "Preliminary Observations of a Novel Topical Oil with Analgesic Properties for Treatment of Acute and Chronic Pain Syndromes : Novel Topical Pain Oil", Pain Practice, 03/03/2010 Publication	<% 1
52	www.medscheme.com Internet Source	<% 1
53	Jaxinthe Siew Kuen ONG. "Risk of hospitalization for upper gastrointestinal tract complications associated with non-selective non-steroidal anti-inflammatory drugs in Malaysia: a retrospective case control study", APLAR Journal of Rheumatology, 11/2004 Publication	<% 1
54	Pineles, L. L., and R. Parente. "Using the Theory of Planned Behavior to Predict Self-Medication with Over-the-Counter Analgesics", Journal of Health Psychology, 2012.	<% 1

55	benthamopen.com Internet Source	<% 1
56	Theron, Andre, and Jerome Loveland. "Birth Prevalence of Anorectal Malformation in the Referral Area for the University of the Witwatersrand Tertiary Hospitals, South Africa", European Journal of Pediatric Surgery, 2014. Publication	<% 1
57	Bello, A. E.. "DUEXIS(R) (ibuprofen 800 mg, famotidine 26.6 mg): a new approach to gastroprotection for patients with chronic pain and inflammation who require treatment with a nonsteroidal anti-inflammatory drug", Therapeutic Advances in Musculoskeletal Diseases, 2012. Publication	<% 1
58	Submitted to University of Aberdeen Student Paper	<% 1
59	Submitted to Laureate Higher Education Group Student Paper	<% 1
60	Coppelli, G.. "Gastric effects of the selective cyclooxygenase-2 inhibitor, celecoxib, in the rat", Digestive and Liver Disease, 200404 Publication	<% 1
61	Submitted to University of Durham	

<% 1

62 www.jiasociety.org
Internet Source

<% 1

63 people.fas.harvard.edu
Internet Source

<% 1

64 Bahtiri, Elton, Hilmi Islami, Rexhep Hoxha, Hasime Qorraj-Bytyqi, Sylejman Rexhepi, Kreshnik Hoti, Kujtim Thaçi, Shpetim Thaçi, and Çağla Karakulak. "Esomeprazole use is independently associated with significant reduction of BMD: 1-year prospective comparative safety study of four proton pump inhibitors", Journal of Bone and Mineral Metabolism, 2015.

<% 1

Publication

65 www.scribd.com
Internet Source

<% 1

66 medlib.mef.hr
Internet Source

<% 1

67 biomedlibsearch.com
Internet Source

<% 1

68 "Management of Patients on Nonsteroidal Anti-inflammatory Drugs: A Clinical Practice Recommendation From the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-

<% 1

inflammatory Drugs and Anti-platelet Agents", The American Journal of Gastroenterology, 11/2008

Publication

69	www.divisionofpsychotherapy.org Internet Source	<% 1
70	jiasociety.org Internet Source	<% 1
71	www.ptolemy.ca Internet Source	<% 1
72	wanda.uef.fi Internet Source	<% 1
73	Submitted to Grand Canyon University Student Paper	<% 1
74	meeting.cityofoviedo.net Internet Source	<% 1
75	www.health.gov.au Internet Source	<% 1
76	Submitted to CSU, San Jose State University Student Paper	<% 1
77	etheses.saurashtrauniversity.edu Internet Source	<% 1
78	www.fda.gov Internet Source	<% 1
79	S STANOS. "Minor and Short-Acting Analgesics, Including Opioid Combination	<% 1

Products", Raj s Practical Management of Pain, 1998

Publication

80	Submitted to 8936 Student Paper	<% 1
81	Harald E Vonkeman. "Direct Medical Costs of Serious Gastrointestinal Ulcers among Users of NSAIDs", Drugs & Aging, 2007 Publication	<% 1
82	N.R. Mphahlele. "Pain in ambulatory HIV-positive South Africans : Pain in ambulatory HIV-positive South Africans", European Journal of Pain, 03/2012 Publication	<% 1
83	Ryuichi Iwakiri. "Roles of NSAIDs and aspirin in bleeding peptic ulcers", Clinical Journal of Gastroenterology, 06/2008 Publication	<% 1
84	file.scirp.org Internet Source	<% 1
85	Submitted to CSU, Dominguez Hills Student Paper	<% 1
86	www.drugwarfacts.org Internet Source	<% 1
87	Submitted to La Trobe University Student Paper	<% 1
88	www.nature.com	

	Internet Source	<% 1
89	Prakash, Bhanu Nadig, Prathiba Nayak, Am. "Rational prescription for a dermatologist. (Special Article)", Indian Journal of Dermatology, Jan-Feb 2016 Issue Publication	<% 1
90	archive.org Internet Source	<% 1
91	Submitted to Monash University Student Paper	<% 1
92	Submitted to University of Venda Student Paper	<% 1
93	etd.uovs.ac.za Internet Source	<% 1
94	Submitted to Middlesex University Student Paper	<% 1
95	www.thepresidency-dpme.gov.za Internet Source	<% 1
96	www.livestrong.com Internet Source	<% 1
97	eprints.usq.edu.au Internet Source	<% 1
98	www.clareharding.com Internet Source	<% 1

99	aje.oxfordjournals.org Internet Source	<% 1
100	phcfm.org Internet Source	<% 1
101	geneticsmr.com Internet Source	<% 1
102	www.hsrb.ac.za Internet Source	<% 1
103	www.cured.com Internet Source	<% 1
104	Fujimori, Shunji, Katya Gudis, and Choitsu Sakamoto. "A Review of Anti-Inflammatory Drug-Induced Gastrointestinal Injury: Focus on Prevention of Small Intestinal Injury", Pharmaceuticals, 2010. Publication	<% 1
105	borrelloosi.net Internet Source	<% 1
106	Peura, D.A.. "Prevention of nonsteroidal anti-inflammatory drug-associated gastrointestinal symptoms and ulcer complications", American Journal of Medicine Supplements, 20040906 Publication	<% 1
107	www.google.com Internet Source	<% 1

108	www.alosafoundation.org Internet Source	<% 1
109	Ajuoga, E.. "Use/misuse of over-the-counter medications and associated adverse drug events among HIV-infected patients", Research in Social and Administrative Pharmacy, 200809 Publication	<% 1
110	Submitted to 82561 Student Paper	<% 1
111	Cryer, B.. "Gastrointestinal side effects of nonsteroidal anti-inflammatory drugs", The American Journal of Medicine, 19980727 Publication	<% 1
112	hub.hku.hk Internet Source	<% 1
113	uir.unisa.ac.za Internet Source	<% 1
114	www.gastrosource.com Internet Source	<% 1
115	dgmc.dsdev.co.za Internet Source	<% 1
116	Maggard, Katie R. Hatwiinda, Sisa Harris, Jennifer B. Phiri, Winifreda Kruuner, Annika Kaunda, Kaund. "Screening for tuberculosis and testing for human immunodeficiency virus in Zambian prisons/Depistage", Bulletin	<% 1

of the World Health Organization, Feb 2015
Issue

Publication

-
- | | | |
|-------|---|------|
| 117 | Sung-Hun Lee. "Prescription Pattern of NSAIDs and the Prevalence of NSAID-induced Gastrointestinal Risk Factors of Orthopaedic Patients in Clinical Practice in Korea", Journal of Korean Medical Science, 2011 | <% 1 |
| <hr/> | | |
| 118 | Griffin, M.R.. "Epidemiology of Nonsteroidal Anti-inflammatory Drug-Associated Gastrointestinal Injury", The American Journal of Medicine, 19980330 | <% 1 |
| <hr/> | | |
| 119 | gut.bmjjournals.com | <% 1 |
| <hr/> | | |
| 120 | "PS 0849-1170", Intensive Care Medicine, 09/2006 | <% 1 |
| <hr/> | | |
| 121 | 146.230.128.141 | <% 1 |
| <hr/> | | |
| 122 | www.doms.co.za | <% 1 |
| <hr/> | | |
| 123 | Philip G. Conaghan. "A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity", Rheumatology | <% 1 |

124	apps.who.int Internet Source	<% 1
-----	---	------

125	www.wjgnet.com Internet Source	<% 1
-----	---	------

126	J. Møller Hansen. "Non-Steroidal Anti-Inflammatory Drugs and Ulcer Complications: a Risk Factor Analysis for Clinical Decision-Making", Scandinavian Journal of Gastroenterology, 2/1/1996 Publication	<% 1
-----	---	------

127	Weinstein, Michael S., Ubaldo J. Martin, Aaron D. Crookshank, Wissam Chatila, Gwendolyn B. Vance, John P. Gaughan, Satoshi Furukawa, and Gerard J. Criner. "Mortality and Functional Performance in Severe Emphysema after Lung Volume Reduction or Transplant", COPD Journal of Chronic Obstructive Pulmonary Disease, 2007. Publication	<% 1
-----	--	------

128	Maree, Johanna Elizabeth, Susanna Catharina Dreyer Wright, and Mogalagadi Rachel Makua. "The Management of HIV- and AIDS-Related Pain in a Primary Health Clinic in Tshwane, South Africa", Pain Management Nursing, 2013. Publication	<% 1
-----	---	------

129 Voss, J.G.. "Symptom Burden of Fatigue in Men and Women Living With HIV/AIDS in Southern Africa", Journal of the Association of Nurses in AIDS Care, 200707 <%1
Publication

130 A Kandulski. "Nichtsteroidale Antirheumatika (NSAR) – an der Schnittstelle gastrointestinaler Nebenwirkungen und kardiovaskulärer Risiken", DMW - Deutsche Medizinische Wochenschrift, 08/2009 <%1
Publication

131 Ko, N-Y., H-C. Lee, S-T. Hsu, W-L. Wang, M-C. Huang, and W-C. Ko. "Differences in HIV disclosure by modes of transmission in Taiwanese families", AIDS Care, 2007. <%1
Publication

EXCLUDE QUOTES OFF
EXCLUDE OFF
BIBLIOGRAPHY

EXCLUDE MATCHES < 5 WORDS

APPENDIX 6: Explanatory notes for Turn It In Report

1. Author Guidelines for submission of a manuscript to the South African Pharmaceutical Journal were copied and pasted from Internet site www.sapj.co.za.

2,4,5. Quotation from the reference cited. (Moore 2014), (WHO 1978) , (Quick 2003) and (Bidaut-Russell 2001)