OVERVIEW OF PROTON PUMP INHIBITOR USE:

A MEDICAL SCHEME PERSPECTIVE

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Preface

This dissertation is presented in article format. The findings of the study are presented in chapter four and chapter five as manuscripts, as required by the regulations of the University of KwaZulu-Natal.

This dissertation consists of five chapters as follows:

Chapter 1: Provides an introduction and explains the rationale and significance of the study. The aims, objectives, and methodology of the study are also highlighted.

Chapter 2: Provides an overview of the methodology used to conduct the study.

Chapter 3: Comprises existing literature and highlights the appropriate indications and dangers of misuse of PPIs.

Chapter 4: Manuscript I entitled, "An overview of proton pump inhibitor usage by members of four medical schemes in South Africa'' was written according to the author's guidelines and submitted for publication to INQUIRY: The Journal of Health Care Organization, Provision and Financing.

Chapter 5: Manuscript II entitled, ''The cost of acute and over-the-counter proton pump inhibitor usage on four medical schemes'' was written according to the author's guidelines and submitted for publication to INQUIRY: The Journal of Health Care Organization, Provision and Financing.

Chapter 6: Provides a summary of the findings, future recommendations, limitations, and strengths of the study with a general conclusion.

Annexures: Presents a data analysis supplement.

Declaration 1: Dissertation submission

This is to certify that the contents of this dissertation are the original work of:

Student: Kajal Mohanlal (214504633)

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Date: 19/06/2023

As the student's supervisor and co-supervisors, we have approved this dissertation for submission.

Supervisor: Prof. Varsha Bangalee

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Date:

Co-Supervisor: Prof. Frasia Oosthuizen

Signed: _____

Date:

Declaration 2: Plagiarism

I, Kajal Mohanlal, declare that:

1. The research reported in this dissertation, except where referenced, is my original work.

2. This dissertation has not been submitted for any degree or examination at any other university.

3. This dissertation does not contain other persons' data, pictures, graphs, or other information unless specifically acknowledged as being sourced from other persons.

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This is to certify that the contents of this thesis are the original work of Miss Kajal Mohanlal and as the candidate's supervisor/ co-supervisors, I have approved this thesis for submission.

Signed:

Prof. Varsha Bangalee: _____ Date: _____

Prof. Frasia Oosthuizen: _____ Date: _____

Declaration 3: Ethical approval

Ethical approval for this study was obtained from the Biomedical Research and Ethics Committee (BREC) at the University of KwaZulu-Natal (UKZN). Reference number: BREC/00004235/2022 - Annexure 1. Permission from Mediscor PBM was also obtained from the Chief Operating Officer – Annexure 2.

Declaration 4: Manuscript publication

My contribution to the project was as follows:

Kajal Mohanlal: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results, manuscript preparation as well as writing and compiling the dissertation.

The contributions of others to the project were as follows:

Prof. Varsha Bangalee: Supervisor – supervision of the concept of the study, the review, and editing of the manuscripts and dissertation.

Prof. Frasia Oosthuizen: Co-Supervisor – supervision of the concept of the study, the review, and editing of the manuscripts and dissertation.

Dedication

I dedicate this achievement to my amazing mother and late father, for it is their continuous love, encouragement, support and guidance throughout my life that has inspired me to conquer my greatest battles and biggest fears. I am also eternally grateful to Pumeshen Pillay for encouraging and supporting me through my most difficult moments.

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List of acronyms and abbreviations

DoH	Department of Health
GERD	Gastroesophageal reflux disease
IV	Intravenous
OTC	Over-the-counter
PBM	Pharmaceutical benefit management
PMB	Prescribed Minimum Benefit
PPI	Proton pump inhibitor
SAHPRA	South African Health Products Regulatory Authority
WHO	World Health Organization

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Abstract

Background

Proton pump inhibitors (PPIs) are highly effective and safe drugs for the treatment of acid-related disorders. However, their easy availability over-the-counter (OTC) often results in the misuse of these drugs. Inappropriate prescribing practices also lead to overutilization, leading to potential long-term adverse effects and rising cost implications on medical schemes. This study aims to provide an overview of PPI misuse and the financial implications on medical schemes in South Africa.

Method

Retrospectively, all acute and OTC PPI claims from four different medical schemes from January 2021 to December 2021 were extracted from an electronic database of a pharmaceutical benefit management organization. A total of 268 537 claims made by 81 566 patients were included in the study. The data obtained were recorded on Excel® and included patient age, sex, generic entity including strength and quantity claimed, prescriber and provider types, month claimed, benefit applicable and the cost reimbursed by the medical scheme per claim in South African Rands. Descriptive and analytical measures were used to evaluate the frequency and duration of PPI usage, provide an overview of the safe indications for use and determine the overall financial impact of PPI usage on medical schemes.

Results

Five different PPI generic entities were analyzed (pantoprazole, omeprazole, lansoprazole, rabeprazole and esomeprazole). PPIs were claimed at an average of 8 times within the twelve-month period per patient. There was a significant correlation between the patient's age and the duration of therapy ($p < 0.001$). Omeprazole (34%), pantoprazole (25%) and esomeprazole (24%) were the most frequently utilized generic entities. More than half of the PPIs claimed were prescribed by general practitioners. Lansoprazole 15 mg, omeprazole 10 mg and 20 mg and pantoprazole 20 mg are available for OTC usage. OTC pharmacy claims made up 13.99% of the total PPI claims submitted. The total cost to the medical schemes was R20 715 453,58, of which high-dose esomeprazole accounted for 30.08%. Two of the four medical schemes implemented an annual quantity limitation on PPIs of 90 tablets or capsules per year effective from 2023.

Conclusion

Despite clear indications for safe use, PPIs are being overutilized on a long-term basis and for inappropriate indications. De-prescribing of PPIs in the elderly, especially high-dose esomeprazole, should be considered when re-evaluating patients to prevent overutilization. Authorized prescribers and pharmacists play an essential role in reducing PPI expenditure and discouraging PPI misuse by prescribing only according to national guidelines for appropriate indications and treatment duration, encouraging the use of cost-effective generics and alternative therapies, and educating patients on healthy lifestyle measures for the long-term management of acid-related disorders. The cost of PPIs to medical schemes in South Africa is currently very high and increasing steadily each year. The costs to medical schemes can be further reduced by implementing benefit design restrictions on PPI reimbursement.

Chapter 1: Introduction

Chapter one provides the overall context for the study. The background, problem statement and rationale for the study are mentioned. The aim, objectives, and a brief methodology are also included.

1.1. Background

Proton pump inhibitors (PPIs) were first introduced in the late 1980s (Vanderhoff and Tahboub, 2002) and are successfully used in the treatment of gastric acid-related disorders, including gastroesophageal reflux disease (GORD) and peptic ulcer disease. The mechanism of action involves the irreversible inhibition of proton pump function (H+/K+ ATPase, found in the highly acidic lumen of parietal cells) (Richardson et al., 1998). Parietal cells will then need to produce new proton pumps, or activate resting pumps, in order to resume gastric acid secretion (Playford & Podas, 1999).

Proton pump inhibitors are highly effective in treating acid-related disorders. despite the low risk of gastric cancer secondary to hypergastrinemia and achlorhydria, theyare considered as safe drugs when used appropriately (Atkins et al., 2013). A typical short course of PPI treatment for a period of two to twelve weeks is usually recommended for the relief of symptoms of GORD and other associated oesophageal lesions. Treatment after this time period should be discontinued, unless maintenance therapy is indicated (Farrell et al., 2017).

Over the years, the safety and effectiveness of PPIs have resulted in their overutilization in multiple treatment settings, from ambulatory care to over-the-counter (OTC) usage (Heidelbaugh et al., 2010). Overutilization of PPIs refers to the excessive usage of these drugs for indications which are often undefined or inconsistent with their registered indications, or for durations which are longer than necessary for the treatment of minor ailments.

Over-the-counter drugs are defined as “medicines sold directly to a consumer without a requirement for a prescription from a healthcare professional” (Millar, 2018). The availability of OTC medicines, i.e. Schedule 1 and 2, has provided citizens with an easily accessible and cost-effective solution to treating minor ailments as an alternative to paying consultation fees to a medical doctor.

In South Africa, all medicines are subject to a scheduling process on the basis of the active pharmaceutical ingredients. These schedules are set out in terms of the Medicines and Related Substances Act (Act 101 of 1965). Section 22A of the Act governs the sale and supply of medicines in the country and provides for a graduated system of control of the sale and supply of drugs, ranging from access through retail outlets to complete prohibition of use (Guideline to the Scheduling of Medicines, 2019).

Proton pump inhibitors are classed as Schedule 3 medicines and require a valid prescription from an authorised prescriber. However, certain low-dose PPIs (i.e. lansoprazole 15 mg, omeprazole 20 mg and pantoprazole 20 mg) are available in specified quantities for OTC usage as a Schedule 2 medicine. Despite well-defined indications for use, overprescribing and easy access to OTC PPIs has resulted in the inappropriate use of these drugs, often resulting in long-term usage for invalid indications or minor dyspepsia, and this poses a danger for drug interactions and severe adverse effects (Dharmarajan, 2021).

The COVID-19 pandemic has resulted in widespread reluctance to seek medical treatment out of fear of contracting COVID-19, therefore increasing the usage of easily accessible, OTC remedies. The pandemic has also changed the financial circumstances of many individuals, therefore increasing the need for more affordable and easily accessible healthcare (Karlsson et al., 2021).

Pharmacists play a key role in the safe, appropriate, and effective use of OTC medicines by ensuring that patients receive the correct drug at the correct dosage for the right condition. However, the ease of access to OTC medicines to the public poses the challenge of potential misuse and abuse of these drugs. Misuse of medicine is defined as the use of an inappropriate quantity of a drug or use for an extended duration, beyond recommended guidelines (Hughes et al., 1999). The growing overutilization and misuse of drugs not only poses a danger to the patient, but also comes with costs which rapidly accumulate over time (Atkins et al., 2013).

South Africa's private healthcare system comprises a number of different medical schemes which vary in the extent of coverage and benefits and cover at least 17% of the population (Ramjee et al., 2014). Day-to-day benefits provide members access to OTC medicines; however, a limit is usually set on the amount that members can claim for OTC products. Popular products often claimed from OTC benefits include sleep aids, codeine, painkillers, and

proton pump inhibitors. Many medical schemes make use of benefit design restrictions to aid in preventing overutilization of medicines such as sleeping aids and PPIs through the use of annual quantity limitations, co-payments and formulary lists which only provide reimbursement of cost-effective products (Khumalo et al., 2012). A study conducted in South Africa in 2010 which analyzed retrospective medical scheme claims had demonstrated the effectiveness of policies implemented by healthcare funders to reduce the financial impact of PPI usage on medical schemes through enhancing generic prescribing (Truter et al., 2023). Maintenance therapy with PPIs for patients with dyspepsia accounted for a total expenditure of €64 million under the Community Drugs Schemes in Ireland, an eight-fold increase since 1995 (McGowan et al., 2005).

The overuse of OTC medicines is not exclusively limited to the private healthcare system. South Africa's quadruple burden of disease (maternal, newborn and child health; Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome (HIV/AIDS) and tuberculosis; and violence and injury) places severe strain on the public healthcare system (NCOP, 2016). With severe shortages of staff and medicines and long waiting times in public hospitals and clinics (Buhlungu et al.,2007), many low-income patients are forced to seek alternative, out-of-pocket remedies for minor ailments through OTC medicine. Immunosuppression due to HIV infection is associated an increased risk for *C. difficile* infection. A study conducted to determine the risk factors for *C. difficile* infection showed an increased risk of infection with associated PPI usage in patients with a CD4 count less than 200 cells/mm^3, demonstrating that PPI utilization in South Africa is of great clinical importance due to the existing burden of HIV infection (Imlay et al., 2016).

In some countries, pharmaceutical expenditure constitutes about 60% of the total health expenditure (Truter et al., 2023). The overuse of PPIs contributes to a large portion of the overall pharmaceutical costs. Studies have shown that almost £2 000 000 000 worldwide are being spent on PPIs prescribed without an appropriate indication (Shafi et al., 2011) and there is, therefore, a need to reduce the overutilization of these drugs in third-world countries like South Africa.

1.2. Problem statement

The usage of PPIs around the world is increasing rapidly. While PPIs are considered safe and effective drugs for the management of acid-related disorders when used according to their registered indications, they are often prescribed for inappropriate indications and long-term treatment leading to overutilization. Overutilization of PPIs is associated with various long-term adverse effects, potential drug-drug interactions, and increased healthcare expenditure. There is currently limited data available on the usage of PPIs and the financial impact thereof on medical schemes in South Africa. It is important to identify the factors contributing to the misuse of PPIs, such as lack of knowledge and inappropriate prescribing practices. Health education programmes for healthcare providers and patients, and strict adherence to guidelines for PPI prescribing, can help reduce the misuse of these drugs and promote appropriate use.

1.3. Rationale and significance of the study

Proton pump inhibitors are indicated for the treatment of gastroesophageal reflux disease, peptic ulcer disease, *H. pylori* eradication, Barrett's eosophagitis and short-term management of dyspepsia. Despite these well-defined indications, PPIs are often prescribed or obtained over the counter without a valid rationale for use, leading to a drastic increase in healthcare costs and long-term associated risks such as gastric cancers, malabsorption of certain nutrients, kidney disease and gastrointestinal infections (Atkins et al., 2013). The yearly increase in PPI usage and its associated adverse effects make PPI utilization an important area of research. This study evaluates the extent of PPI usage by members of medical schemes by providing an overview of the frequency of OTC and acute PPI claims submitted by pharmacies and the associated financial impact, through the evaluation of the cost of acute and OTC PPI claims, on four medical schemes in South Africa. Reviewing PPI usage in South Africa will ultimately determine the effect of current prescribing practices, and help to guide healthcare providers, patients and policymakers to improve clinical outcomes while reducing the financial impact on an already overburdened healthcare system.

1.4. Aims and objectives

The aim of the study was to evaluate the extent of PPI usage by members of medical schemes in South Africa. This was achieved through the following objectives:

(i) To review the PPIs available as OTC products and the indications for safe use.
(ii) To determine the number of acute and OTC PPI claims per member of the medical schemes in 2021.
(iii) To compare the results of (ii) to safe indications for use.
(iv) To determine the financial implication of OTC PPI usage on medical schemes.
(v) To assess benefit design restrictions placed by medical schemes as a method of preventing PPI misuse.

Reviewing the current PPI usage in South Africa will help identify and provide greater insight into the potential misuse of these drugs and the financial impact thereof, in order for appropriate measures to be put into place to prevent the overutilization of these drugs for unclear rationale.

Chapter summary

This chapter has provided an outline of the study and the significance of the research, aims and objectives are discussed. The following chapter provides an overview of the methodology used for the study.

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Chapter 2: Methodology

2.1. Study design

A retrospective, cross-sectional quantitative study was conducted to evaluate PPI usage among members of four medical schemes.

The study population includes all members of four medical schemes who have claimed for acute and OTC PPIs between January and December 2021. The study population includes men, women, all age groups, races and demographic attributes.

2.2. Data source

Acute and OTC PPI claim data were extracted from the study site, Mediscor PBM®, a pharmaceutical benefit management organization that specializes in electronic claims processing and the management of medicine benefits for medical schemes and medical insurances in South Africa, serving more than 2.7 million patients.

2.3. Inclusion criteria

- All acute and OTC PPI claims from four different medical schemes between January 2021 and December 2021.
- All age groups and patient demographic types.
- All prescriber and provider types.
- Five generic entities were included in the study. i.e. pantoprazole, lansoprazole, esomeprazole, omeprazole and rabeprazole.

2.4. Exclusion criteria

- All PPI claims approved and funded from chronic benefits.
- Dexlansoprazole and any other PPI generic entities not mentioned above.

2.5. Data collection

The required information was extracted from the Mediscor® claims database for 2021 and the information was downloaded onto a workbook in Microsoft Excel®. The data was extracted through electronic reports run by the company on a routine basis

throughout the year. No validation procedures or potential challenges were encountered, and only the final report was available for the purpose of this study. All data extracted were already anonymized and no patient-identifiable information was obtained. The data extracted included patient age, active ingredient and dosage form of PPI claimed, quantity, month claimed, benefit applicable, prescriber and provider types. The costs of each generic entity to the scheme were also extracted from the data. Medical scheme benefit design rules for reimbursement of PPIs were also obtained and analyzed. Since only pharmacy claims data was extracted, the indications for therapy remained unknown. The duration of therapy was determined based on the quantity of tablets or capsules claimed, and the number of claims per member during the year.

2.6. Data analysis

The information was coded, analyzed and presented in the form of tables and graphs. The number of claims per patient for 2021, including patient age groups, as well as prescriber and provider types were analyzed to identify the extent of PPI usage and overall duration of treatment. The results were then compared to the recommended duration of treatment for short-term indications. The cost breakdown for each benefit and generic entity was used to determine the financial implication for medical schemes.

2.7. Data management

The data collected were stored on a password-protected computer and backup hard-drive. The data will be removed upon dissemination of results.

2.8. Strengths of the study

- **Large sample size:** Retrospective quantitative studies are able to review large amounts of data, allowing for statistical analysis and generalization to larger populations.
- **Cost-effective:** Retrospective studies are generally less expensive and time-consuming than prospective studies, and data are available without incurring any costs.

- **Access to existing data:** The study uses existing claims data and is useful in evaluating patterns and trends in healthcare utilization.

2.9. Weaknesses of the study

- **Limited control over data quality:** Researchers have little control over the quality of data being analyzed as it has already been collected for other purposes.
- **Limited ability to establish causation:** Retrospective studies are not designed to establish causation as they rely on pre-existing data and cannot account for confounding variables.
- **Risk of bias:** Retrospective studies can be susceptible to selection bias, as data may only include patients who received certain treatments or services. There may also be misclassification bias as the data may be incomplete or incorrect.

2.10. Confidentiality

All information was kept strictly confidential. Patient's names and medical scheme membership details were coded. Individual patient consent forms were not required as only anonymized, retrospective data were utilised.

2.11. Ethical approval

Ethical approval was obtained from the Biomedical Research and Ethics Committee (BREC) located at the University of KwaZulu-Natal (UKZN); Ethical approval number: BREC/00004235/2022 – Annexure 1).

Chapter summary

This chapter has provided an outline of the methodology used for the research. The following chapter provides a theoretical basis for the study.

Chapter 3: Literature review

3.1. Introduction

Chapter three provides an overview of access to OTC medicines and usage of PPIs by members of medical schemes in South Africa. An in-depth review of the appropriate indications for proton pump inhibitors is provided, including the potential adverse effects associated with their misuse. This chapter will also highlight the easy accessibility to OTC medicines, and the role and responsibility of pharmacists in preventing the misuse of OTC medicine, specifically PPIs.

3.2. Access to OTC medicines

Medicines in South Africa are subjected to a scheduling process based on the active pharmaceutical ingredients they contain. In terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), a 'scheduled substance' is defined as any medicine or other substance prescribed by the Minister under section 22A (Guideline to the Scheduling of Medicines, 2019). The primary consideration when scheduling a substance is its safety profile in relation to the therapeutic indications for use. Substances may be listed in one or more of the eight schedules based on the dosage form, route of administration, strength, indication, dose, duration of treatment or a combination of these factors (SAHPRA, 2023). Schedule 0 substances are available are available off the shelf, without prescription or pharmacist intervention. Schedule 1 and 2 are available through intervention from a pharmacist, and are known as OTC medicines (Fasken, 2018).

Self-medication is defined by the World Health Organization (WHO) as the use of drugs to self-diagnosed disorders or symptoms, or the intermittent or continued use of prescribed drugs for chronic or recurrent disease or symptoms even after the duration prescribed is finished ("WHO Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-Medication: General Information," 2000). The ability to access self-medication, or OTC medicines, without a valid prescription provides patients with an opportunity to self-manage their symptoms through the assistance of their

community or retail pharmacy, and allows individuals to play an active role in the management of their health (Cooper, 2013). However, the availability of OTC medicines to the general public places tremendous responsibility on pharmacists to ensure the appropriate and safe use of OTC medicines, refer patients to medical practitioners when necessary, and efficiently identify possible cases of OTC drug misuse.

Drug misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines (World Health Organization, 2006). The misuse of OTC medicines places a huge burden on health and social services in South Africa. The relatively low cost and easy procurement of OTC medicines allow them to be easily misused (Myers et al., 2003).

The easy accessibility of OTC medicines without a prescription increases the likelihood of misuse of these drugs and is of growing concern in South Africa. A literature review was conducted to examine the extent of OTC medicine misuse in South Africa (Myers et al., 2003). The review identified several studies that reported high rates of OTC medicine misuse, particularly among low-income populations. Misuse was associated with factors such lack of knowledge, poor health literacy and self-medication practices (Dada et al., 2015; Kawuma et al., 2021; Myers et al., 2003). The findings have highlighted the need for targeted public education campaigns and stricter regulation of OTC medicines, with possible regulatory or policy changes to prevent misuse and possible harm (Dada et al., 2015).

A study conducted by Richard J. Cooper (2013) entitled, “Over-the-counter medicine abuse – a review of the literature” reviewed literature between 1990 and 2011 and found that OTC medication abuse was identified in many countries, and five key groups of most widely abused medicines were identified:

- Codeine-containing medicines
- Cough medicines
- Sedative antihistamines

- Decongestants
- Laxatives

At least 8.78 million South African citizens are covered by a medical scheme which, depending on the extent of benefits which vary between scheme and option, include an OTC medicine benefit as an element of the benefit design (Ncube et al., 2017). According to a study conducted by Padayachee et al. (2020) investigating the usage of OTC medicines by members of two medical schemes in South Africa between January and December 2015 found that 58-68% of the members included in the study had accessed OTC medicines through the OTC medicine benefit of their medical scheme in 2015.

3.3. Appropriate use of PPIs

Proton pump inhibitors are one of the most effective classes of drugs used for gastric acid-related conditions through the irreversible inhibition of gastric H+/K+ ATPase (Sachs et al., 2006), and are among the most frequently prescribed classes of drugs in the world due to their ideal combination of high efficacy and low toxicity (Forgacs & Loganayagam, 2008).

Omeprazole was the first PPI to be introduced in 2002, and prescriptions for PPIs had doubled within five years of omeprazole's introduction. Thereafter, esomeprazole, pantoprazole, lansoprazole and rabeprazole were introduced commercially. However, studies have shown that between 25% and 70% of patients taking these drugs have no appropriate indication (Forgacs & Loganayagam, 2008).

A study conducted in 2016, reviewing articles evaluating the use of PPIs in the PubMed® database and Cochrane Library, found the following indications for which the use of PPIs was undisputed (Mössner, 2016):

• *Helicobacter Pylori* eradication (PPI + amoxicillin + clarithromycin, or PPI + clarithromycin + metronidazole).

• Short-term treatment of gastroesophageal reflux disease and long-term prevention of recurrence.

- Healing of gastric and duodenal ulcers.
- Secondary prevention of NSAID-induced gastroduodenal lesions.
- Treatment of Barrett's oesophagitis.

Table 1 indicates the recommended dosages and duration of use for various PPIs for treatment and prevention of the abovementioned indications according to the Monthly Index of Medical Specialities (MIMS) (Snyman, 2021).

Table 1: Appropriate dosing guidelines for various PPIs as per MIMS

Proton pump inhibitor	**Recommended dosage and duration of treatment**
Omeprazole	**Duodenal ulcers:** 20 mg daily for 2-4 weeks. 40mg once daily when refractory to other treatments. 10mg for prevention of relapse - increase to 20-40 mg once daily if necessary. Above regimen in combination with appropriate antibiotic for duodenal ulcers associated with *H. pylori* infection **Gastric ulcers and reflux oesophagitis:** 20 mg daily for 4-8 weeks. When refractory to other treatments, 40 mg once daily may be effective. Long term reflux oesophagitis management: 10mg once daily - increase to 20-40 mg once daily if necessary. In severe /symptomatic recurring reflux oesophagitis, continue with 20 mg once daily **NSAID-associated gastro-duodenal lesions with or without continuous NSAID treatment:** 20 mg once daily. If not healed within 4 weeks, continue treatment for a further 4 weeks **NSAID-associated gastro-duodenal lesions and dyspeptic symptoms prophylaxis:** 20 mg once daily **Symptomatic gastro-oesophageal reflux disease:** 10-20 mg once daily. Investigate further if symptom control not achieved after 2 weeks treatment at 20 mg once daily

	Zollinger-Ellison syndrome: Initially 60 mg daily. Individualize and continue as long as clinically required. Dosages over 80 mg daily to be administered in 2 divided doses **Severe ulcerative reflux oesophagitis:** 10-20 kg – 10 mg once daily increasing to 20 mg once daily if necessary. >20 km – 20 mg once daily increasing to 40 mg once daily if necessary
Pantoprazole	**Mild gastroesophageal reflux disease:** 20 mg/day for 4-week period. If healing not achieved, extend for further 4 weeks **Long-term management and prevention of gastroesophageal reflux disease relapse:** 20 mg once daily. Increase to 40 mg once daily if relapse occurs and reduce back to 20 mg once daily after relapse heals **Duodenal ulcers:** 40 mg once daily for 2-4 weeks. Use in combination with appropriate antibiotic when associated with *H. pylori* **Gastric ulcers and reflux oesophagitis:** 40 mg once daily for 4-8 weeks **Zollinger-Ellison syndrome:** Initially 80 mg daily, thereafter titrate as necessary. Administer daily doses above 80 mg in 2 divided doses
Esomeprazole	**Erosive reflux oesophagitis:** 40 mg once daily for 4 weeks. If not healed or if symptoms persist, continue for an additional 4 weeks **Relapse prevention of healing oesophagitis:** 20 mg once daily **Symptomatic gastroesophageal reflux disease:** If oesophagitis not present, administer 20 mg once daily. Subsequent symptom control can be achieved on a demand regimen of 20 mg once daily. If symptom control not achieved after 4 weeks, investigate further **Continuous NSAID therapy:** 20-40 mg once daily ***H. pylori*-associated ulcers and relapse prevention:** 20 mg twice daily in combination with amoxicillin 1 g and clarithromycin 500 mg for 7 days
Lansoprazole	**Gastric ulcers:** 30 mg once daily for up to 8 weeks **Duodenal ulcers:** 30 mg once daily for up to 4 weeks. With appropriate antibiotics as part of eradication programme for H. pylori positive ulcers

	Oesophagitis due to gastroesophageal reflux: 30 mg once daily for 4 weeks. Repeat for further 4 weeks if necessary **Gastroesophageal reflux prevention:** Maintenance – 15 mg once daily for maximum 1 year **Functional dyspepsia:** Adults - 15-30 mg once daily for 2-4 weeks. Elderly - Max daily dose: 30 mg **Heartburn and hyperacidity:** 15 mg daily for up to a maximum of 14 days. Consult practitioner should symptoms persist/worsen
Rabeprazole	**Active duodenal ulcers/active benign gastric ulcers:** 20 mg once daily in the morning for 4-6 weeks. Some patients may require an additional 4-6 weeks to achieve healing. **Erosive/ulcerative gastroesophageal reflux disease:** 20 mg once daily for 4-8 weeks **Gastroesophageal reflux disease maintenance:** 10-20 mg daily for a maximum of 12 months. Efficacy not established for periods exceeding 12 months **Symptomatic gastroesophageal reflux disease:** 10 mg once daily in patients without oesophagitis. Investigate further if control not achieved after 4 weeks. Once symptoms resolve, administer 10 mg once daily when necessary **Zollinger-Ellison Syndrome and other hypersecretory conditions:** 60 mg once daily titrating up to 120 mg once daily based on individual needs. Doses up to 100 mg may be administered as a single dose. Dosage of 120 mg to be divided into 60 mg twice daily. Continue treatment as long as clinically necessary. ***H. pylori* eradication:** Part of the eradication program with appropriate antibiotics. Recommended combination (all administered twice daily for 7 days): Rabeprazole 20 mg + Clarithromycin 500 mg + Amoxicillin 1 g

Despite the above well-defined indications for PPI usage, inappropriate prescribing practices and access to OTC PPIs, along with a lack of information, have resulted in an alarming increase in the use of PPIs without documented appropriate indication, or continuation of use without documentation of re-evaluation of upper gastrointestinal tract symptoms (Jaynes & Kumar, 2019).

Many aspects should be taken into consideration before prescribing a PPI, including the following (Atkins et al., 2013):

(i) The dosage, duration of treatment and clinical reasons for using a PPI, including an assessment of the appropriateness of treatment.

(ii) Considering the appropriateness of using an H2-receptor antagonist before commencing with a PPI.

(iii) Evaluation of the patient's other medication which may be contributing to the symptoms of gastro-oesophageal reflux disease.

3.4. Potential dangers of PPI overutilization

Since their first introduction, PPIs have become the treatment of choice for acid-related disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease (Horn, 2000). However, emerging evidence suggests that PPIs are being overprescribed, leading to various adverse effects (Schoenfeld & Grady, 2016). The following literature review aims to examine the implications of PPI overutilization.

3.4.1. Prescription rate and overuse

The use of PPIs had risen by almost 456% within ten years since their first introduction in the 1980s (Guda et al., 2004). Numerous studies have reported a high prevalence of PPI prescriptions which were found to be non-compliant with clinical guidelines. A study conducted in the United States of America found that only 39% of PPI prescriptions were compliant with clinical guidelines (Eid et al., 2010), while in Australia, 77.5% of PPI prescriptions reviewed in a hospital setting did not comply with clinical guidelines, with more than half being prescribed for incorrect indication, dosage and duration of treatment (Ksiądzyna et al., 2015). Despite being safe and effective drugs when used appropriately, their wide distribution leads to overuse, inappropriate dosing and grossly extended durations of

treatment resulting in adverse effects such as increased intestinal dysbiosis leading to increased susceptibility to infections, risk of osteoporosis, nutritional deficiencies and drug interactions (Corleto et al., 2014; Sheen & Triadafilopoulos, 2011).

3.4.2. Long-term use and dependence

PPIs can be used on either a long-term basis (chronic) or short-term basis for the treatment of minor gastric-related ailments (i.e. acute usage). In both cases, a prescription from a registered healthcare practitioner is required. Drug dependence is a state of psychic or physical dependence on a drug following administration of the drug on a periodic or continuous basis (Eddy et al., 1965). PPIs suppress gastric acid secretion, and cause rebound gastric acid hypersecretion upon withdrawal, creating dependency (Metz, 2008). A study conducted in Italy found that 79% of patients were on long-term PPI therapy, with 47% being used for inappropriate indications (Lombardo et al., 2011). The ongoing acid secretion feedback mechanism creates a need for ongoing treatment to control symptoms, with higher initial doses being more likely to initiate this response and lead to adverse effects.

3.4.3. Alternative therapies

Due to growing concern expressed by physicians and patients over the long-term use of PPIs and the associated adverse effects, alternative therapeutic strategies for the treatment of gastric acid-related disorders are being explored. Alternative non-pharmaceutical approaches to managing acid-related disorders include lifestyle changes, smoking cessation, weight loss, surgical and endoscopic techniques (Fass, 2012). Antacids may provide an effective alternative for the short-term relief of dyspepsia, however the long-term use of non-absorbable antacids has been shown to hinder the gastrointestinal absorption of phosphorus, leading to osteomalacia and rickets (Shetty et al., 1998). H_2-receptor antagonists provide an effective alternative for the relief of GERD, however long-term use has been associated with tachyphylaxis (Howden, 1993).

3.4.4. Cost implications

Together with potential adverse effects, the financial implication of PPI overutilization should also be considered. The costs incurred using PPIs by individuals, especially on a long-term basis, are extensive. PPIs are one of the most prescribed drug classes in the world, costing

England £425 000 000, and £7 000 000 000 globally in 2006 (Shafi et al., 2011). Opportunities exist to decrease the overall PPI expenditure through adherence to recommended dosing guidelines and the use of step-down approaches in asymptomatic patients where appropriate (Hughes et al., 2009). Promotion of healthier lifestyles and use of alternative therapies such as H_2-antagonists and antacids may also be beneficial in cost reduction.

3.4.5. Conclusion

The overuse of PPIs is prevalent throughout the world and is associated with several clinical and financial implications. These negative implications can be avoided through the promotion of healthier lifestyles, adopting step-down approaches in asymptomatic patients, adhering to clinical guidelines and protocols, and considering alternative therapies such as H_2-antagonists and antacids.

3.5. Adverse effects and drug-drug interactions

Proton pump inhibitors affect the absorption and metabolism of other drugs through their interaction with adenosine triphosphate-dependent P-glycoprotein, or with the cytochrome P450 (CYP) enzyme system, resulting in drug-drug interactions.

A literature search screening 408 publications performed to provide a summary of currently available clinical data on drug-drug interactions involving OTC medicines revealed that PPIs and alternative therapies such as antacids and H_2-antagonists were among the main groups of medicine responsible for drug-drug interactions (Scherf-Clavel, 2022).

The chronic use of high-dose PPIs affects the absorption of calcium, magnesium and vitamin B12, as the presence of gastric acid facilitates the ionization and assimilation of dietary calcium and the release of food-bound vitamin B12 (Strand et al., 2017).

The following drug-drug interactions are of concern:

- **Clopidogrel**

  Clopidogrel is an antiplatelet agent used for the secondary prevention of cardiovascular events in patients with coronary artery disease, acute coronary syndromes and ischaemic stroke (Bouziana & Tziomalos, 2015). Despite the reduction in the risk of gastrointestinal bleeding with the use of PPIs in patients treated with clopidogrel, recent attention was placed on the in-vitro interaction between omeprazole and clopidogrel. Data indicates that the interaction involves the competitive inhibition of the CYP2C19 isoenzyme. The inhibition of CYP2C19 by PPIs prevents the conversion of clopidogrel to its active metabolite. Omeprazole is the most potent CYP2C19 inhibitor in its class. Previous retrospective analyzes have shown an increase in adverse cardiovascular outcomes when PPIs and clopidogrel are used concomitantly (Norgard et al., 2009).

- **Mycophenolate mofetil**

  Mycophenolate was developed as a potential antibiotic, antineoplastic and anti-psoriatic drug, and has now become the immunosuppressant of choice for preventing allograft rejection after organ transplantation (Kofler et al., 2010). Gastrointestinal side effects are common after solid organ transplantation, resulting in the need for treatment with a PPI. Mycophenolate exposure is reduced with co-administration of PPIs due to reduced mycophenolate dissolution rates at higher gastric pH, with pantoprazole being the most frequently cited interacting PPI (Knorr et al., 2014).

- **Methotrexate**

  Methotrexate is an antimetabolite used in the treatment of severe psoriasis, rheumatoid arthritis and certain neoplastic diseases (Xanodyne Pharmacal, 2003). Studies have shown that PPIs interfere with methotrexate clearance (particularly at high doses) leading accumulation of methotrexate and its metabolite, resulting in methotrexate toxicity (Bezabeh et al., 2012).

- **Antiretrovirals**

  Among antiretroviral drugs, rilpivirine and atazanavir are the most vulnerable to interactions with acid-suppressants, as they require a lower gastric pH for optimum dissolution and absorption. The dosage of PPIs co-administered with atazanavir in treatment-naïve patients should not exceed the equivalent of omeprazole 20 mg daily. The use of atazanavir is not recommended in patients already on long-term PPI therapy. Rilpivirine levels are lowered by up to 40%, hence the co-administration of rilpivirine and PPIs is contraindicated (Faragon, 2020). These interactions are especially significant to South Africa. With 5.7 million individuals infected with HIV, South Africa has one of the highest HIV infection rates in the world (CDC, 2016).

The following long-term adverse effects are of concern:

- **Increased fracture risk**

Several studies have indicated a potential association between PPI usage and increased fracture risk. An increase in gastrin production and hypochlorhydria are the two main mechanisms affecting bone re-modelling, mineral absorption and muscle strength, which contributes to an increase in the risk of fractures and the development of osteoporosis in PPIs users (Thong et al., 2019). A study conducted in the United Kingdom in 2006, including more than 13 000 patients, revealed an increase in the incidence of hip fractures with PPI use that exceeded one year, and especially increased in those who had received high-dose PPIs (Yang et al., 2006). In 2010, the United States Food and Drug Administration (FDA) required all PPI manufacturers to include warnings of possible risk of fractures of the hip, wrist and spine when used at high doses (more than once daily) and/or for a long duration (greater than one year) (Strand et al., 2017).

- **Risk of gastric cancer**

Hypergastrinaemia as a result of reduced gastric acid secretion from long-term PPI usage has been associated with gastrointestinal neoplasia (Scherf-Clavel, 2022). Hyperplasia of enterochromaffin-like have also been observed in long-term users of PPIs, and an increased incidence of atrophic gastritis in patients with *Helicobacter pylori* infection using long-term PPIs (Kuipers et al., 1996; Lamberts et al., 1993).

- **Risk of infection**

The presence of gastric acid serves as a means of inactivating ingested micro-organisms, and preventing infectious organisms from reaching the intestine.Previous studies have shown that chronic use of PPIs is a risk factor for rotavirus, influenza virus, norovirus and Middle East respiratory syndrome coronavirus infections (Zhou et al., 2017). The United States FDA also announced that overexposure or prolonged use of a PPI may be associated with higher risk of *C. difficile* infection (FDA, 2012). Click or tap here to enter text.Studies have also demonstrated a higher incidence of bacterial gastroenteritis with current PPI therapy (Garcia Rodríguez & Ruigómez, 1997; Neal et al., 1996). The possibility of long-term PPI usage as a risk factor for severe COVID-19 infection was also explored, and thus a greater need to balance the benefits and risks of unnecessary long-term PPI use during the ongoing pandemic (Charpiat et al., 2020).

- **Acute interstitial nephritis**

In February 2021, the South African Health Products Regulatory Authority (SAHPRA) released an important medicine safety notice informing healthcare professionals of an increased risk in subclinical acute nephritis associated with the use of PPIs leading to chronic renal inflammation and reduced renal function (SAHPRA, 2021). Delay in diagnosis and continuation of PPI use can lead to chronic renal failure (Yang et al., 2017).

- **Masking symptoms of underlying conditions**

Early symptoms of gastric cancers are usually indistinguishable from other benign acid-related disorders, and patients are often prescribed antisecretory therapy such as PPIs resulting in the resolution of symptoms without further endoscopic investigation. The rapid control of dyspepsia through PPI usage often leads the patient and prescriber to underestimate the importance of the symptoms. Usage of PPIs prior to endoscopic investigations also risks early lesions becoming less visible, leading to missed diagnoses of more serious underlying conditions (Griffin & Raimes, 1998).

The abovementioned concerns highlight the necessity for pharmacists and clinicians to conduct good history-taking and investigate patient use of chronic, OTC and recreational drugs, especially in vulnerable populations such as the elderly and HIV-positive individuals. Clinician awareness of drug interactions and long-term adverse effects with PPIs are essential to prevent toxicity and treatment failure due to sub-optimal drug exposure as a result of altered gastric pH (McCabe et al., 2007).

3.6. The cost of PPI overutilization

A retrospective medical record review conducted in Michigan to determine the prevalence and economic effect of inappropriate PPI use revealed a total cost of $233 994 of OTC PPIs between February 2006 and January 2007 (Heidelbaugh et al., 2010). Another study conducted with non-ICU patients revealed that an annual cost saving of over $35000 at a single hospital could be possible if precautions were put in place to reduce the non-compliant prescribing of PPIs (Nasser et al., 2010).

Billions of rands are spent annually on OTC medicine in South Africa. The misuse of PPIs, both OTC and those inappropriately prescribed by a medical practitioner, have negative cost implications on medical schemes in South Africa. According to a study which investigated the utilization of OTC medicines by members of two medical insurances in South Africa, the cost of OTC products accessed by the beneficiary or recommended by a pharmacist was higher than when prescribed by a medical practitioner (Padayachee et al., 2020). However, the overall cost of OTC and acute PPI claims to medical schemes may vary according to the benefit

structure and specified limits. Most medical schemes implement restrictions through co-payments, formulary lists and annual quantity limitations to effectively manage healthcare costs. These limitations usually restrict the maximum reimbursable quantity of specific classes of drugs, or aim to reduce expenditure through the reimbursement of only certain cost-effective generic entities.

Chapter Summary

This chapter highlighted the ease of access to OTC medicines in South Africa, and its implication on the misuse of these medicines, paying particular attention to OTC PPIs. The chapter also focused on the appropriate uses and dosing of various PPIs, and the cost implication of OTC PPI misuse and inappropriate prescribing of PPIs on medical schemes in South Africa.

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Chapter 4: Manuscript I

Introduction

Chapter four reviews the usage of PPIs by members of four medical schemes in South Africa. The study quantifies the claims for OTC and acute PPIs, comments on the trends and compares the results to the safe indications for use.

The chapter is presented in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN).

A complement of the data extracted is presented in Annexure 3.

The manuscript has been submitted for publication to the journal – INQUIRY: The Journal of Health Care Organization, Provision and Financing. (see Annexure 5). This chapter has been written, formatted, cited, and referenced according to the journal's submission guidelines. The journal instructions to the author can be viewed in Annexure 4.

An overview of proton pump inhibitor usage by members of four medical schemes in South Africa

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Word count: 4061

Abstract

Background

Access to over-the-counter (OTC) medicines provides an easy and cost-effective method of self-diagnosis and treatment. However, it can lead to misuse of certain medicines, e.g. proton pump inhibitors (PPIs). Despite well-defined indications for usage, inappropriate prescribing practices and access to OTC PPIs have resulted in an alarming increase in use without documented appropriate indication, or continuation of use without documentation of re-evaluation of upper gastrointestinal tract symptoms.

Aim

The study aims to quantify the usage of PPIs by analyzing the acute and OTC PPI claims submitted to medical schemes and comparing the results to the safe indications for use.

Setting

A pharmaceutical benefit management (PBM) organization specializing in electronic claims processing and the management of medicine benefits on behalf of medical schemes in South Africa. The study only pertains to four medical schemes' members for the period of January to December 2021.

Methods

Retrospectively, all acute and OTC PPI claims from four different medical schemes from January 2021 to December 2021 were extracted from an electronic database. Claims made by 81 566 patients were included in the study. The patient age, sex, month of claim, generic entity including strength and quantity claimed, prescriber and provider information was recorded on Excel®. Descriptive and analytical measures were used to analyze patient information and the frequency of PPI claims per patient and per generic entity to determine the frequency and appropriateness of PPI usage.

Results

A total of 268 537 claims made by 81 566 patients were reviewed. Omeprazole (34%), pantoprazole (25%) and esomeprazole (24%) were the most frequently utilized. Lansoprazole (17%) and rabeprazole (0.67%) were the least frequently utilized. PPIs were claimed at an

average of 8 times per patient in 2021 (SD = 3.94). There was a significant correlation between the patients' age and the duration of therapy ($p < 0.001$).

Conclusion

Many patients are being prescribed PPIs for inappropriate indications and extended treatment durations, which do not correlate with their registered indications. Prescribers and pharmacists need to play a greater role in preventing PPI misuse by ensuring that these drugs are prescribed according to their registered indication.

Introduction

Since their introduction more than 25 years ago, proton pump inhibitors (PPIs) have shown to be safe and effective agents for the management of several acid-related disorders through the inhibition of active parietal cell acid secretion (Strand et al., 2017). However, an increasing list of complications resulting from the long-term use of PPIs has been reported over the past decade (Malfertheiner et al., 2017).

Acid reflux is a common complaint received in the pharmacy setting, and the number of PPIs available over-the-counter (OTC) provides a fast and cost-effective relief (Boardman & Heeley, 2015). This places responsibility on the pharmacist to make an accurate diagnosis, counsel patients on the proper use of PPIs, identify signs indicating more severe disease for which referral to a medical practitioner is necessary, as well as identify the potential misuse of PPIs. A study conducted to determine the safety of appropriate OTC PPI use, determined that OTC PPIs are generally safe and effective when used in accordance with label instructions (Johnson et al., 2017).

In South Africa, the currently available OTC PPIs are indicated for short-term regimens of a maximum of 14 days. The FDA recommends no more than three courses of treatment for heartburn with PPIs available as OTC preparations per year, for no longer than two weeks each (Ksiądzyna et al., 2015). However, their easy accessibility often results in usage for unnecessarily extended courses, which can lead to a variety of adverse outcomes associated with prolonged PPI use (Gaisinskaya et al, 2021). These adverse outcomes include calcium, magnesium and vitamin B12 malabsorption, interactions with other chronic medicines such as clopidogrel and increased infection and fracture risk (Gaisinskaya et al, 2021; Strand et al., 2017).

Aside from OTC usage, PPIs are also commonly prescribed by medical practitioners as symptomatic treatment without clear indications or for unregistered indications, with almost one-third of the patients who start PPI treatment continuing to refill their prescription without evident indication for maintenance therapy (Ksiądzyna et al., 2015).

The primary aim of this study was to assess the extent of PPI usage by registered members of medical schemes in South Africa. The main objective of the study was to quantify the various types of PPIs claimed electronically from OTC and acute benefits. The secondary objective was to comment on the frequency of the OTC and PPI claims per patient and compare them to the safe indications and durations of use.

Research methods and design

Study design and setting

This retrospective cross-sectional study utilized claims data spanning over a period of 12 months (January 2021 to December 2021) extracted from a pharmaceutical benefit management (PBM) organization located in Centurion, Gauteng.

Study population and sampling strategy

All claims for acute and OTC PPIs from four different medical schemes in South Africa were included in the study. Acute and OTC PPI claims for members of the four medical schemes of all ages, including men and women were included in the study. A total of 268 537 claims from 81 566 patients were included in the study.

Data collection

Electronic claims data from four different South African medical schemes were obtained from a database provided by a PBM organization.

The data extracted were downloaded from a central database onto an Excel® spreadsheet and included the following elements:

- Month of claim
- Member age
- Sex
- Generic entity

- Benefit category
- Quantity and days' supply
- Provider and prescriber type
- Cost to scheme

All data were kept confidential, with all names and member numbers being removed. All patient identifiers were coded, and records were kept on a password-protected device. Individual patient informed consent was not required for data collection as only anonymized, retrospective data were extracted.

Data analysis

Analytical and descriptive measures were used to describe patient age groups, sex, prescribers and providers, and PPI generic entities. The frequencies and means were calculated to describe PPI usage patterns among the participants included in the study. The quantitative data values are represented as distribution tables and bar charts. The relationship between patient age group and the frequency of PPI claims was investigated using the Chi-square test. The level of significance was set at $\alpha=0.05$.

Eliminating bias

The probability for biased selection was eliminated by including every acute and OTC PPI claim from four different medical schemes from January to December 2021. Data were extracted electronically and not performed by anyone involved in prescribing or providing PPIs.

Ethical approval

Ethical approval was sought from the relevant bodies:

- Biomedical Research and Ethics Committee (BREC) located at the University of KwaZulu-Natal (UKZN) (Annexure 1).

Permissions:

- Chief Operating Officer (COO) at the study site (Annexure 2).

Results

Demographic and general characteristics

The frequency of PPI claims stratified by patient age group and sex for 81 566 members with a total of 268 537 acute and OTC PPI claims are shown in Table 1. Claims for female members comprised 56.68% of the total claims. The average member age was 55 years, with a minimum age of 0 and a maximum age of 102. Claims for patients under the age of 40 years comprised 18.43% of the total number of claims (N = 268 537). Most acute and OTC PPI claims (n = 219 053) were claimed for members over the age of 40 years.

Correlations investigated

The correlation between patient age and number of PPI claims was investigated:

$$X^2\ (1, n = 268\ 537) = 8936,\ p < 0.001$$

The p-value indicates that older patient age is strongly associated with more frequent PPI usage.

The Shapiro-Wilk test of normality was conducted to determine whether the number of claims per patient is normal distributed. The result concluded that the data is normally distributed for the number of claims per patient (p=0.5).

Table 1: Frequency of PPI claims, stratified by age group and sex, N = 268 537

Demographics	Number of claims N	Number of patients in age group	Average no. of claims per patient, per age group	% of total acute and OTC PPI claims
Age (years)				
0-2	1 261	758	2	0.47
3-12	1 723	1281	1	0.64
13-39	46 500	22 602	2	17.32
40-59	101 601	32 233	3	37.84
≥ 60	117 452	24 692	5	43.74
Sex				
Female	157 566			58.68
Male	110 971			41.32

The various PPI generic entities, indications for use and quantity claimed are shown in Table 2. A total of 268 537 acute and OTC PPI claims were submitted by 81 566 members of four different medical schemes in 2021, with an average of 8 claims per patient (SD = 3.94), indicating a treatment duration of 240 days. At least 66.52% of the claims submitted were for a quantity of 30 tablets or capsules.

Table 2: PPI generic entities, indications for use and quantities claimed, N = 268 537

PPI generic entity	Indication	Strength of active ingredient (mg)	Route of administration	No. of claims	%
Pantoprazole	GORD, duodenal/gastric ulcers, reflux oesophagitis, Zollinger-Ellison syndrome	20	Oral	19 832	7.39
		40	Oral	45 732	17.03
		40	Intravenous	707	0.26
			Total:	**66 271**	
Omeprazole	GORD, duodenal/gastric ulcers, dyspepsia prophylaxis, Zollinger-Ellison syndrome, severe ulcerative reflux oesophagitis	10	Oral	1 156	0.43
		20	Oral	82 930	30.88
		40	Oral	6 754	2.52
		40	Intravenous	10	0
			Total:	**90 850**	

Lansoprazole	Duodenal/gastric ulcers, oesophagitis due to GORD, GORD prevention, dyspepsia, hyperacidity	15 30	Oral Oral	**Total:**	24 435 21 037 **45 472**	9.10 7.83
Esomeprazole	GORD, treatment and prevention of reflux oesophagitis, continuous NSAID therapy, *H. pylori*-associated ulcers and relapse prevention	2.5 5 10 20 40 40	Oral Oral Oral Oral Oral Intravenous	**Total:**	420 632 641 15 879 46 281 277 **64 130**	0.16 0.24 0.24 5.91 17.23 0.10
Rabeprazole	Duodenal/gastric ulcers, GORD, Zollinger-Ellison syndrome, *H. pylori* eradication	10 20	Oral Oral	**Total:**	439 1 375 **1 814**	0.16 0.51

Legend (Table 2):
GORD: Gastroesophageal reflux disease
H. pylori: Helicobacter pylori

The percentages of each generic entity claimed are shown in Figure 1. Overall, omeprazole was the most frequently claimed PPI (34%), closely followed by pantoprazole (25%) and esomeprazole (24%). Lansoprazole was the fourth-frequent PPI claimed (17%), while rabeprazole was the least frequently claimed (0.68%).

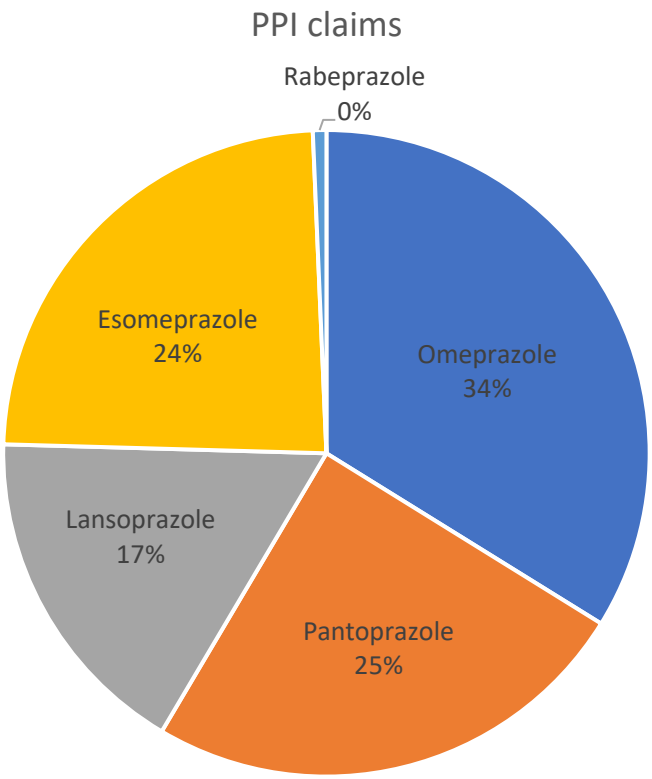


Figure 1: Generic entities claimed

The distribution of claims between acute and OTC benefits is depicted in Table 3. The majority of claims were submitted as acute claims (86.01%), indicating that the majority of these PPIs were prescribed by a medical practitioner. OTC pharmacy claims made up 13.99% of the total claims submitted.

Table 3: Distribution of acute and OTC claims

Benefit category	Frequency	%
Acute	230 965	86.01
OTC	37 572	13.99

Figure 2 shows the distribution of claims according to the prescribers. General practitioners were the leading prescribers of PPIs (66%), followed by specialists (15.41%) and pharmacies (14.02%). All other prescribers cumulatively made up less than 5% of the total claims submitted.

Figure 2: PPI claim distribution according to prescriber

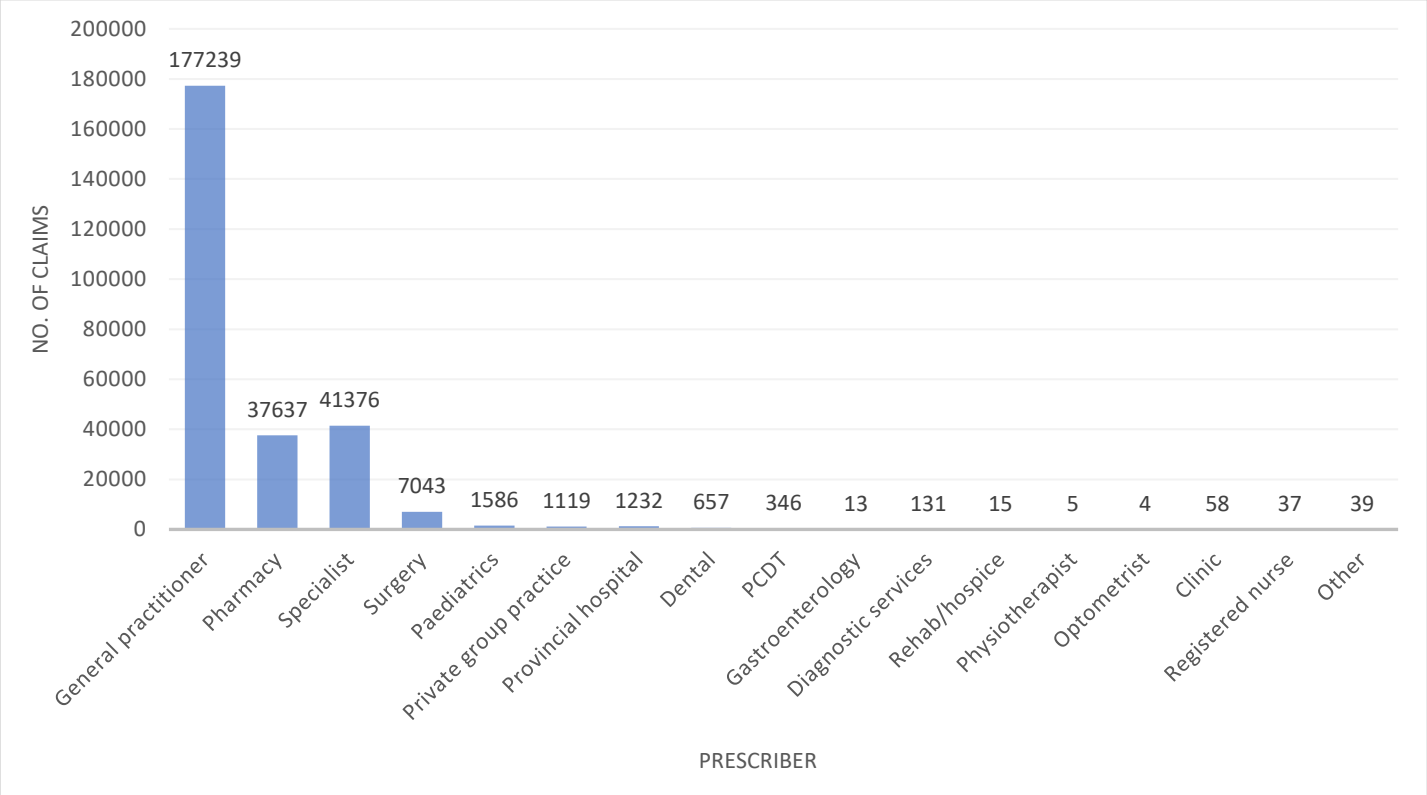
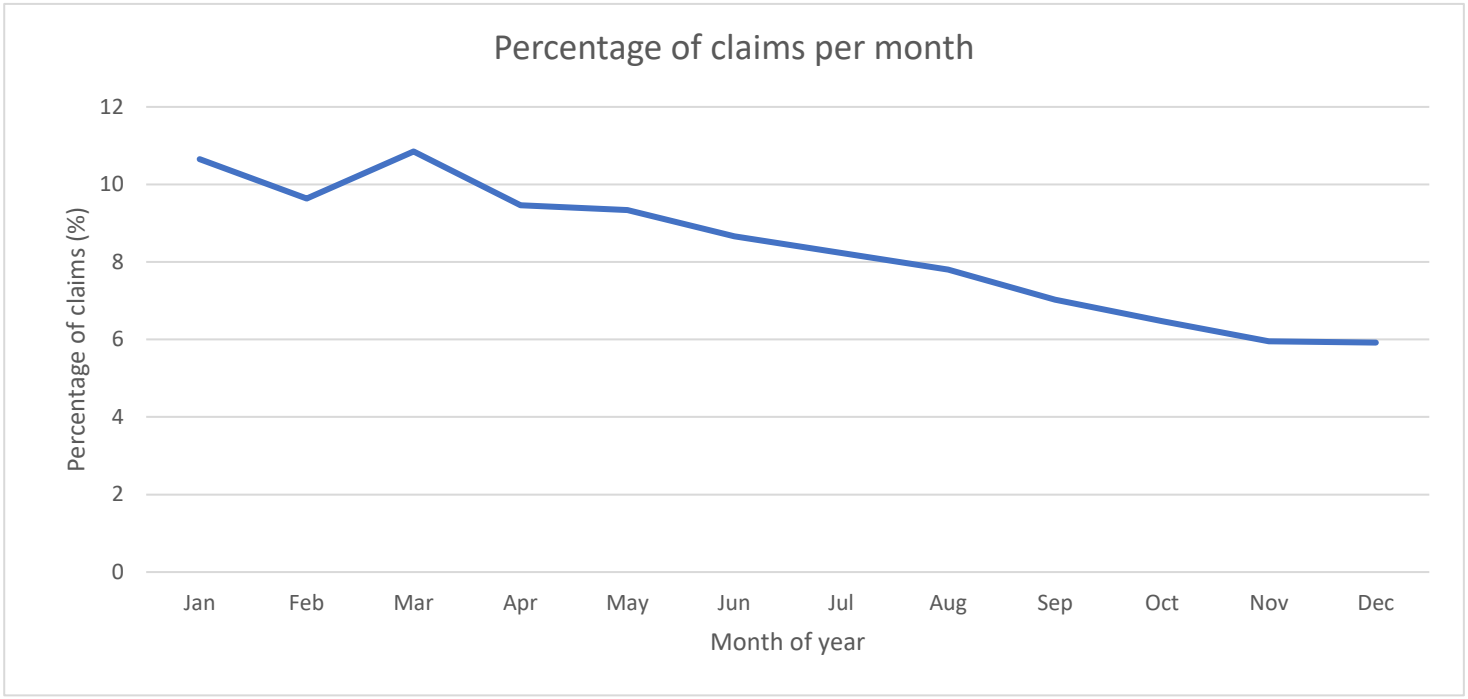


Figure 3 depicts the percentage of PPI claims for each month of the year. It is noted that claims were most frequently submitted in the first quarter of the year and steadily declined thereafter.

Figure 3: Percentage of PPI claims per month



Discussion

The aim of the study was to review the PPIs available and evaluate the frequency of acute and OTC claims submitted to medical schemes for these drugs. However, it is important to note that the actual diagnoses for the PPIs claimed were unknown; hence the number of claims and the strength of PPI claimed per patient were compared to the recommended duration of treatment for short-term indications to determine the appropriateness of PPI usage and make a comparison with their safe indications for use.

A significant correlation was established between patient age and number of PPI claims submitted. As the patient age increases, the number of PPI claims increases ($p < 0.001$), with the greatest number of PPI claims being submitted for patients over the age of 40 years. A total of 43.74% of the total claims were submitted for patients over the age of 60 years. Diseases of the gastrointestinal tract become more common and severe with advancing age (Franceschi et al., 2009). Another possible reason is that the elderly are often prone to a greater burden of polypharmacy and are often prescribed PPIs without a valid indication (Voukelatou et al., 2019). Polypharmacy also exposes elderly patients to more drug-drug interactions and various adverse events (Teramura-Grönblad et al., 2010), and increases the risk of acid-related disorders such as upper gastrointestinal bleeding through the long-term

use of NSAIDS and bisphosphonates. Recent concerns were raised over the potential suppression of symptoms of more serious underlying conditions with prolonged PPI usage, such as gastric cancer and the development of gastric carcinoids (Naunton et al., 2000). A study conducted in the United Kingdom, which compared two patient scenarios, found that empirical treatment in the first patient delayed diagnosis of gastric cancer by almost four years due to complete resolution of symptoms after each course of PPI received. The second patient received a ten-day course of omeprazole after presenting with epigastric discomfort and was found asymptomatic on endoscopy. Multiple biopsies thereafter revealed intramucosal adenocarcinoma (Wayman et al., 1998). Due to the susceptibility of the elderly to adverse drug reactions, drug-drug interactions and masking of more serious underlying conditions, it is imperative that caution be exercised by prescribers and pharmacists to ensure that PPIs are only prescribed to elderly populations for a clear rationale.

In this study, 58.68% of all claims for PPIs were for women, however, this finding cannot be generalised to the general population. A study conducted in Australia revealed that more women initiated and used PPIs than men (Daniels et al., 2020). Gastrin is a peptide hormone responsible for gastric mucosal growth, motility and secretion of hydrochloric acid into the stomach (Prosapio et al., 2023). A sustained increase in gastrin levels has been shown in several studies as a result of long-term acid-suppression by PPIs (Ligumsky et al., 2001; Maton, 1991). Chronic elevation of gastrin levels is thought to be associated with gastrointestinal cancers. Recent studies demonstrated significantly higher baseline gastrin levels in women, and a study conducted by the National University of Iceland in 2020 which aimed to evaluate the short-term effect of esomeprazole on gastrin levels and evaluate possible sex-related differences, found that the increase in serum gastrin levels after administration of esomeprazole was not sex-related (Helgadóttir et al., 2021).

Five different proton pump inhibitors were included in this study – omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole. Since the discovery of omeprazole in 1979, the dispensing of proton pump inhibitors has increased (Connelly, 2016). It was expected that omeprazole and lansoprazole would constitute the majority of the claims due to their cost-effectiveness. A study conducted in England in 2015 revealed that omeprazole was not only the most frequently prescribed PPI (30 100 000 prescriptions), but also the second most commonly dispensed medicine overall (Connelly, 2016). Unsurprisingly, omeprazole

constitute the majority of the claims in this study, though lansoprazole was the third most frequently claimed PPI.

The popular use of omeprazole is also a reason for prescribers and pharmacists to be more wary of possible drug-drug interactions, as PPIs are frequently prescribed to patients receiving dual antiplatelet therapy (DAPT) following myocardial infarction and other cardiovascular events (Ogawa & Echizen, 2010). Proper history-taking is not always carried out by pharmacists (Hanya et al., 2007); however in the case of the medical schemes included in the study, benefit design restrictions are put into place to reject claims for omeprazole which are submitted within a close date-range to clopidogrel, thus warning the dispenser of possible drug-drug interactions.

In this study, high dose PPIs were defined as generic entities containing at least 40 mg of the active ingredient. Standard doses refer to the recommended dosages as per treatment guidelines for common indications. Low-dose PPIs refers to initation dosages, or dosages below those recommended as per treatment guidelines. The number of claims for high-dose PPIs (i.e. pantoprazole 40 mg, omeprazole 40 mg and esomeprazole 40 mg) were considerably higher than for low-dose and standard-dose PPIs (i.e. pantoprazole 20 mg; omeprazole 10 mg, 20 mg and 40 mg; esomeprazole 2.5 mg, 5 mg, 10 mg and 20 mg; lansoprazole 15 mg and 30 mg and rabeprazole 10 mg and 20 mg). High-dose PPIs generally have little proven clinical advantage over standard-dose PPIs in many clinical situations (Targownik et al., 2007). High-dose PPIs are used long-term for conditions such as Barrett's oesophagitis and Zollinger-Ellison syndrome. In most cases, the use of high-dose or double-dose (i.e. twice daily) PPIs is recommended for the treatment of mild and moderate gastroesophageal reflux disease, erosive reflux oesophagitis and duodenal and gastric ulcers including *H. pylori* eradication for a maximum of eight weeks, followed by a short course of low-dose PPI if necessary.

Medicaid®, a health insurance in the United States of America offered to low-income residents, defined overutilization as usage of a PPI for longer than the FDA-recommended time period of 4-8 weeks (HCA, 2017). According to the data collected, each patient submitted an average of 8 claims per year, the majority of which were claimed consecutively (i.e. weeks duration of therapy).

The PPI claims data revealed that PPI usage was highest in the first quarter of the year (31.14%), and thereafter steadily declined. This is most likely due to the depletion of medical aid funds as the year progresses, and therefore cannot be seen as a reflection of the true pattern of PPI usage throughout the year as cash purchases were not included in this study. Another possible reason for increased usage during the first quarter may be due to overindulgence and poor eating habits over the festive season.

More than half of the PPIs claimed (66%) were prescribed by general practitioners. This may be due to the fact that general practitioners are usually easily accessible and the first point of contact when experiencing any illness. According to a study conducted in England investigating the escalating costs associated with the rapid increase in prescribing of PPIs, three explanations were put forward. The first explanation states that PPIs are being prescribed inappropriately by general practitioners. The second explanation states that patients are putting pressure on their general practitioners to prescribe specific drugs, including PPIs, due to the use of the National Health Service. The third explanation states that a large number of patients are using PPIs as a means of continuing with unhealthy lifestyles, a likely precursor of gastric-related issues (Grime et al., 2001). General practitioners should ideally act as gatekeepers, perform initial diagnostic tests and refer patients to a specialist when necessary (Haastrup et al., 2016).

Only 13 PPI claims submitted for reimbursement to the four medical schemes during 2021 were prescribed by gastroenterologists. The low incidence may be due to the lack of referral to a gastroenterologist, or the fear of undergoing invasive diagnostic procedures such as gastroscopy and colonoscopy during the COVID-19 pandemic. Other possibilities may include the high cost of these diagnostic procedures. Gastroscopy, generally performed as an out-patient procedure, has a very low complication rate. A study performed in Turkey indicated a 59.32% drop in the number of patients undergoing gastrointestinal endoscopy following the first case of COVID-19 (Cakcak et al., 2022).

The claims data were split according to the applicable medical scheme benefit. Acute PPI claims included those claimed in conjunction with a valid authorised prescriber's practice number. OTC claims included all PPI claims submitted by pharmacies as pharmacist-initiated therapy, or which were acquired as self-medication.

Over-the-counter pharmacy claims made up 14.02% of the total PPI claims submitted. With COVID-19 preventative and control measures implemented throughout 2021, many patients became increasingly reliant on their community pharmacy for medical advice, with many individuals failing to seek follow-up care with their medical practitioner due to fear of infection (Akour et al., 2021). Unconfirmed information relating to possible health benefits of certain products was also circulated via social media, causing a surge in the unsafe use of OTC medicines (Kretchy et al., 2021).

Some studies indicate that the use of PPIs was associated with a nominal, but statistically significant increase in risk of COVID-19 infection, poorer outcomes and mortality (Fatima et al., 2022). Gastric acid acts as a barrier, preventing viruses from entering the rest of the gastrointestinal tract. This barrier is disrupted by even a single dose PPI, raising the gastric pH level from the normal range of 1.5-3.5 to over 6.0, therefore allowing viruses to enter the gastrointestinal tract and increasing the risk of infection (Price & Treacher, 2021).

It was also found that the maximum quantity of PPIs claimed was sometimes much higher than the usual recommended dosage. The maximum quantity of pantoprazole 20 mg and esomeprazole 2.5 mg claimed was 120, while the maximum quantity of omeprazole 20 mg, lansoprazole 30 mg and esomeprazole 40 mg was 180. This is most likely due to patients claiming advance supplies of medicine before leaving the country, and may not necessarily be attributed to overdosage. At least 66.52% of the claims were for a quantity of thirty tablets or capsules, with an average of three claims per patient being submitted consecutively, indicating an average duration of 34 weeks of PPI therapy, significantly longer than the usual recommended treatment duration of four to eight weeks for the short-term management of acid-related disorders.

Implications and recommendations

Overall, the use of PPIs is generally safe and effective for the treatment and prevention of gastric acid-related conditions when used according to their registered indications and duration of treatment. However, it is evident that further studies should be conducted to determine the safety of long-term high-dose PPI usage. Prescribers and pharmacists need to

exercise vigilance, and ensure that PPIs are prescribed only for appropriate indications for the shortest possible duration at the lowest effective dose, especially in the elderly.

Limitations

There are a few limitations to the study. The demographic data that could be extracted from the claim records were limited, and the study was unable to analyze each patient's medical conditions and concurrent medicine usage individually to ascertain inappropriate PPI usage. The diagnoses for all PPIs prescribed were also unknown. The study was only carried out through the assessment of medical scheme claims, and the results can therefore not be extrapolated to the public sector or patients who are not members of a medical scheme or medical insurance. Despite these limitations, the study contributes to and builds on the research that currently exist on PPIs.

Conclusion

This study provides an overview of acute and OTC PPI usage by members of four medical schemes. The ease of access to OTC PPIs has allowed these drugs to be misused, and greater responsibility should be taken by pharmacists to ensure that OTC PPIs are used only for the intended duration of treatment and ensure that patients whose symptoms remain unresolved are appropriately referred for the relevant diagnostic tests. Despite the lack of solid clinical evidence regarding the harmful effects of long-term PPI usage, efforts need to be made by prescribers to ensure that prescriptions for PPIs strictly comply with their registered indications for use to prevent the overutilization of these drugs. The use of PPIs to support unhealthy lifestyle habits must be discouraged by healthcare professionals to prevent the misuse of these drugs.

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Competing interests

The authors have declared that no competing interests exists.

Authors' contributions

KM was the principal researcher. KM, FO and VB were responsible for the overall study design and conceptualization. KM conducted the data analysis and interpretation with the assistance of VB and FO. KM wrote the article, which was reviewed by all authors.

Funding information

No funding was required for this study.

Data availability statement

The data supporting the findings of this study are available from the corresponding author (KM) upon reasonable request.

Disclaimer

The content presented is solely the responsibility of the authors and does not represent the official views of any other organization.

Chapter summary

Chapter four reviewed the prevalence of PPI usage through the analysis of acute and OTC claims from four different medical schemes. It also highlighted the appropriate indications and duration of use of PPIs, and the potential risks of overutilization of these drugs.

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Chapter 5: Manuscript II

Introduction

Chapter five reviews the cost of acute and over-the-counter (OTC) proton pump inhibitor (PPI) usage on four medical schemes and reviews different benefit design restrictions implemented as a method of reducing the cost impact of PPI misuse on the scheme.

Chapter five is in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN).

A complement of the data extracted is presented in Annexure 3.

The manuscript has been submitted for publication to the journal - INQUIRY: The Journal of Health Care Organization, Provision and Financing (see Annexure 5). This chapter has been written, formatted, cited, and referenced according to the journal's submission guidelines. The journal instructions to the author can be viewed in Annexure 4.

The cost of acute and over-the-counter proton pump inhibitor usage on four medical schemes

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Word count: 3679

Abstract

Background

There are 72 different open and restricted medical schemes in South Africa, providing varying medicine reimbursement benefits to their members. Proton pump inhibitors (PPI) are among the most prescribed medicines worldwide and have significant financial implications on medical schemes due to overutilization and over-the-counter (OTC) misuse. Medical schemes are now implementing limitations to discourage inappropriate prescribing and reduce the financial burden of PPIs.

Aim

This study aimed to determine the cost implication of acute and OTC PPIs on medical schemes through the analysis of acute and OTC PPI claims and assess benefit design restrictions implemented to reduce overutilization.

Setting

A pharmaceutical benefits management (PBM) organization specializing in electronic claims processing and the management of medicine benefits, located in Centurion, Gauteng.

Methods

Retrospectively, all acute and OTC claims for omeprazole, lansoprazole, esomeprazole, rabeprazole and pantoprazole from four different medical schemes from January 2021 to December 2021 were extracted from an electronic database. The cost of PPI claims made by 81 566 patients were included in the study. The data obtained included patient age, sex, month of claim, generic entity including strength and quantity, prescriber and provider type. The cost reimbursed by the scheme was recorded on Excel®, and descriptive and analytical measures were used to analyze patient information and claims data to determine the cost to the medical schemes.

Results

Acute and OTC PPIs cost the four medical schemes a total of R20 715 453,58. Esomeprazole had the highest cost implication to the schemes (R7 881 885,37), and 30.08% of the claims were for high-dose omeprazole. OTC PPIs accounted for 4.59% of the overall cost. Approximately 66% of the PPIs claimed were prescribed by a general practitioner. Two out of

four of the medical schemes in this study have since implemented an annual quantity limitation on PPIs of 90 tablets or capsules per year.

Conclusion

PPIs have a significant cost implication to medical schemes annually due to overutilization, potential misuse and inappropriate prescribing practices. Authorised prescribers and pharmacists play a vital role in reducing PPI expenditure by prescribing according to registered indications and encouraging the use of cost-effective generics. Medical schemes can also implement additional benefit design restrictions to prevent the long-term use of PPIs without a valid indication.

Introduction

A medical scheme is a type of insurance for which financial coverage for medical treatment and related expenses is provided in exchange for a monthly contribution or premium (CMS, 2023). In South Africa, there are 26 different open medical schemes which are all governed and regulated by the Medical Schemes Act. These schemes vary in the type of coverage benefits and limits, depending on the provider and option selected (Fedhealth, 2023).

Prescribed minimum benefits (PMBs) are a set of defined benefits ensuring that members of medical schemes have access to certain minimum health services regardless of the benefit option selected (CMS, 2023). Gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, Barrett's Esophagitis and other acid-related disorders are not considered as PMB conditions; hence PPIs are funded according to each individual scheme rule.

Since the first introduction of omeprazole, proton pump inhibitors (PPIs) have remained superior in the treatment and prevention of acid-related gastrointestinal disorders and are now among the most prescribed medicines worldwide (Othman et al., 2016). Aside from the numerous risks involved with injudicious long-term PPI usage, these drugs also account for a significant portion of healthcare expenditure (Heidelbaugh et al., 2009).

The direct and indirect costs of treatment of gastroesophageal reflux disease in the United States of America accounted for $9.8 billion in 2000, with both prescription and over-the-counter (OTC) PPIs ranking near the top of the expenditure lists. (Heidelbaugh et al., 2009). The availability of OTC PPIs has allowed patients access to short-term courses of PPIs for relief of mild gastric acid-related symptoms.

Medical schemes manage healthcare risks in an effort to control medical costs. Benefit design refers to decisions made by medical schemes about health services and goods to be funded, as well as the conditions to be met to access funding benefits (WHO, 2023). These decisions are made to reduce unmet needs and improve financial protection through rationing of patient access to healthcare by the use of market prices, funding of priority cost-effective treatments, waiting lists, co-payments and quantity limitations (WHO, 2023). Many medical schemes also make use of formulary lists to promote the use of cost-effective medicines (Khumalo et al., 2012). This allows for the exclusive reimbursement of specific products, and medicines included in the formulary are usually reimbursed in full. Medicines which are not

on the formulary list will either carry an out-of-pocket co-payment or will not be reimbursed by the medical scheme and require self-funding from the patient. These restrictions play a role in discouraging inappropriate prescribing practices and preventing misuse of OTC medicine.

The aim of this study was to assess the financial implication of acute and OTC PPI usage on medical schemes, and to assess the various benefit design restrictions put in place by the schemes to prevent the misuse of PPIs by their members.

Research methods and design

Study design and setting

This retrospective cross-sectional study utilized claims data spanning over a period of 12 months (January 2021 to December 2021) extracted from a pharmaceutical benefit management (PBM) organization located in Centurion, Gauteng.

Study population and sampling strategy

All claims for acute and OTC PPIs from four different medical schemes in South Africa were included in the study. All acute and OTC PPI claims for members of the four medical schemes for all age groups and both men and women were included in the study. A total of 268 537 claims from 81 566 patients were included in the study.

Data collection

Electronic claims data from four different South African medical schemes were obtained from a database provided by a PBM organization.

The data generated were downloaded from a central database onto an Excel® spreadsheet and included the following elements:

- Month of claim
- Member age

- Sex
- Generic entity
- Benefit category
- Quantity and days' supply
- Provider and prescriber type
- Cost to scheme

All data were kept confidential, with all names and member numbers being removed. All patient identifiers were coded, and records were kept on a password-protected device. Individual patient informed consent was not required for data collection as only anonymized, retrospective data were extracted.

Data analysis

The total cost to the scheme per PPI generic entity was calculated from pharmacy claims data obtained from the database of a pharmaceutical benefit management company. The costs incurred per generic entity were also calculated and compared. The means were calculated to describe the average cost to the scheme among the participants included in the study. The quantitative data values are represented as frequency distribution tables and bar charts.

Eliminating bias

The probability for biased selection was eliminated by including every acute and OTC PPI claim from four different medical schemes from January to December 2021. Data were extracted electronically and not performed by anyone involved in prescribing or providing PPIs.

Ethical approval

Ethical approval was sought from the relevant bodies:

- Biomedical Research and Ethics Committee (BREC) located at the University of KwaZulu-Natal (UKZN) (Annexure 1).

Permissions:

- Chief Operating Officer (COO) at the study site (Annexure 2).

Results

Medical scheme characteristics

Table 1 briefly outlines the characteristics of the four medical schemes from which data were obtained. All four schemes comprised of multiple options with varying benefits and limits. This meant that members could claim PPIs at the pharmacy from their acute and OTC benefits provided that sufficient funds were available.

Table 1: Medical schemes and limitations on PPIs

Medical Scheme	No. of options	Quantity limitations on PPIs (2021)	Limitations on PPIs (2022)
A	13	None	None
B	9	None	90 per year
C	6	None	None
D	3	None	90 per year

Cost implication

Table 2 outlines the costs of the various generic entities to the schemes in 2021. A total of 268 537 pharmacy claims were analyzed. The total cost to the schemes was R20 715 453,58. The total South African Rand value only includes amounts that were funded by the scheme, and excludes the cost of rejected claims.

Table 2: Cost of acute and OTC PPIs to four medical schemes in 2021

Generic entity	Strength (mg)	Route of administration	Average cost per acute claim (ZAR)	Standard deviation	Number of claims in 2021	Actual cost to medical schemes in 2021 (ZAR)
Pantoprazole	20	Oral	145,70	70,87	19 832	878 695,60
	40	Oral	208,82	104,02	45 732	3 170 142,00
	40	IV	62,82	40.18	707	16 710,53
		TOTAL:			66 271	**4 065 600,60**
Omeprazole	10	Oral	197,97	98,43	1 156	78 115,29
	20	Oral	198,94	95,22	82 930	5 311 782,12
	40	Oral	359,92	182,74	6 754	966 374,00
	40	IV	90,42	41,26	10	180,83
		TOTAL:			90 850	**6 356 452,24**
Lansoprazole	15	Oral	125,33	44,59	24 435	738 742,60
	30	Oral	199,85	98,28	21 037	1 495 072,01
		TOTAL:			45 472	**2 233 814,61**
Esomeprazole	2.5	Oral	387,91	191,90	420	38 015.,14
	5	Oral	359,56	162,28	632	40 271,10
	10	Oral	328,18	161,18	641	50 867,68
	20	Oral	276,84	139,36	15 879	1 510 432,35
	40	Oral	390,00	193,54	46 281	6 230 200,00
	40	IV	95,47	58,74	277	12 029,10
		TOTAL:			64 130	**7 881 815,37**
Rabeprazole	10	Oral	216,57	97,60	439	24 038,83
	20	Oral	358,41	172,28	1 375	154 833,40
		TOTAL:				**178 872,23**
GRAND TOTAL:						**20 715 453,58**

Figure 1 depicts the cost breakdown per PPI generic entity. The costs were further broken down according to the dosage of PPI claimed – i.e. Low/standard/high-dose. In this study, high dose PPIs were defined as generic entities containing at least 40 mg of the active ingredient. Standard doses refer to the recommended dosages as per treatment guidelines for common indications. Low-dose PPIs refers to initation dosages, or dosages below those recommended as per treatment guidelines. The data was not tested for normality.

Despite being the second most frequently claimed PPI, esomeprazole had the highest cost implication to the schemes, costing a total of R7 881 815,37, followed closely by omeprazole at R6 356 452,24. The average cost per claim for all strengths of esomeprazole was higher than that of omeprazole.

Rabeprazole was the least frequently claimed PPI and had the lowest cost implication to the schemes at R178 872,23.

Claims for oral high-dose esomeprazole made up 79.20% of the total esomeprazole cost to the schemes, as well as 30.08% of the total cost of acute and OTC PPIs.

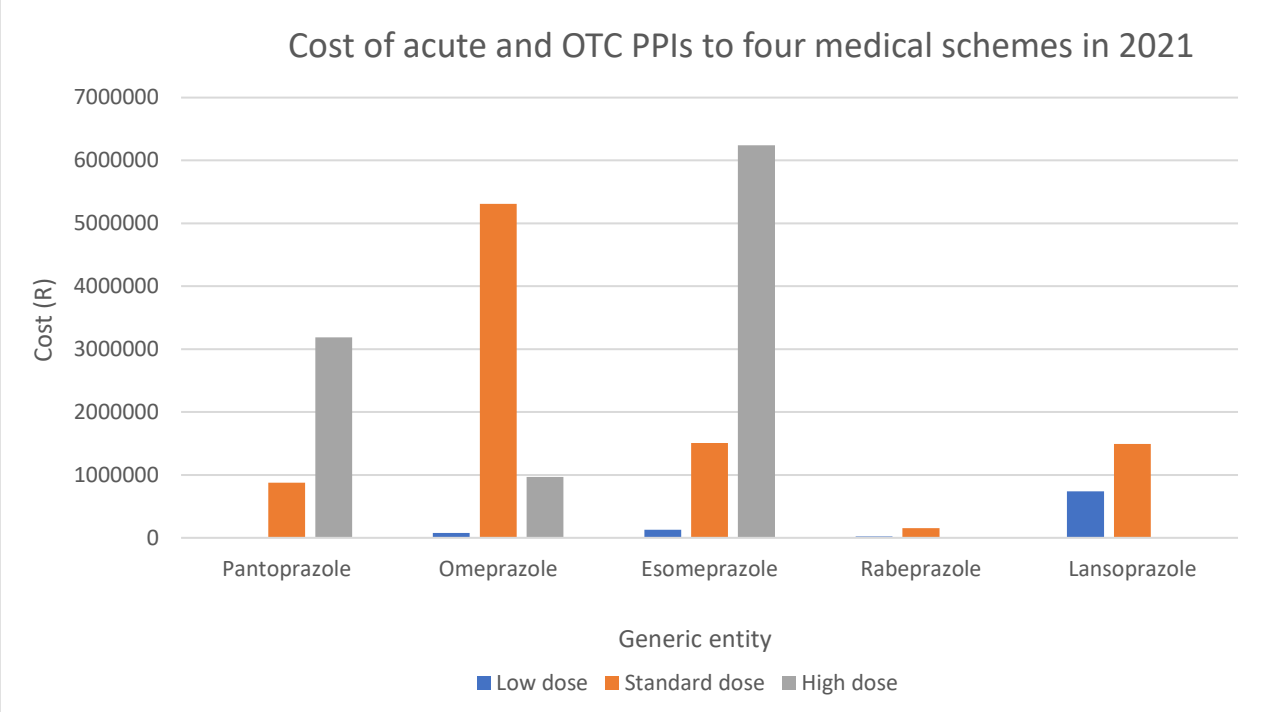

Figure 1: Cost breakdown of PPIs to medical schemes in 2021

Figure 2 provides a breakdown of the total cost of OTC claims to the schemes in 2021. A total of 37 572 OTC claims were submitted, of which only 13 105 claims were either partially or fully funded by the scheme. A total of R951 006,90 was funded by the medical schemes. Lansoprazole 15 mg made up more than half the cost (R502 737,10 from 19 562 claims), followed by omeprazole 20 mg (R397 381,60 from 15 466 claims). Omeprazole 10 mg (R4 864,97 from 238 claims) and pantoprazole 20 mg (R46 023,23 from 2306 claims) made up the smallest proportion of the cost.

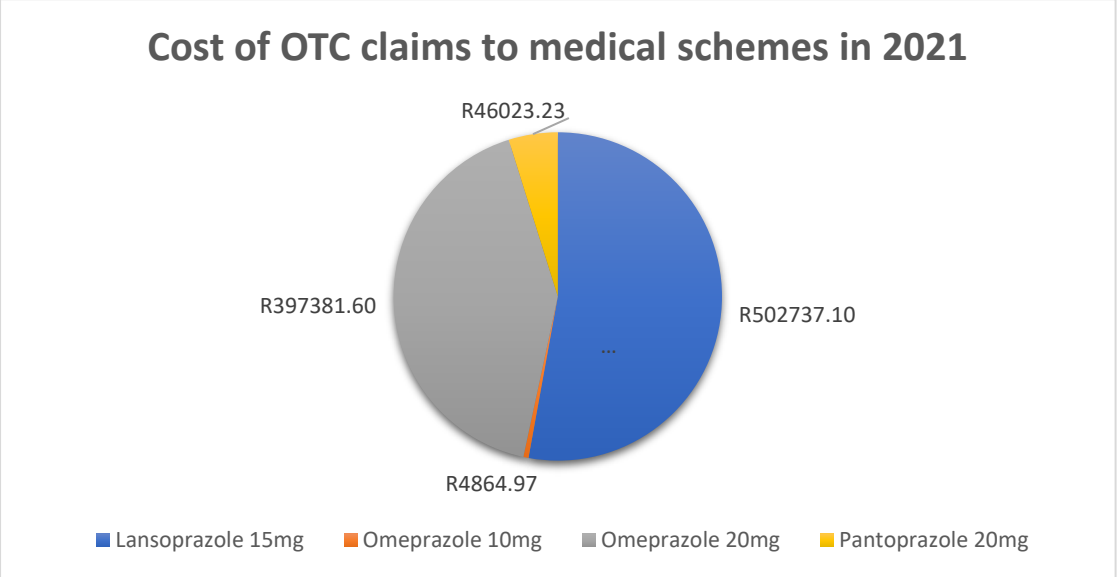

Figure 2: Cost breakdown of OTC PPI claims to medical schemes in 2021

Figure 3 depicts a breakdown of the total acute and OTC PPI cost per dosage type – i.e. Low-dose, standard-dose and high-dose.

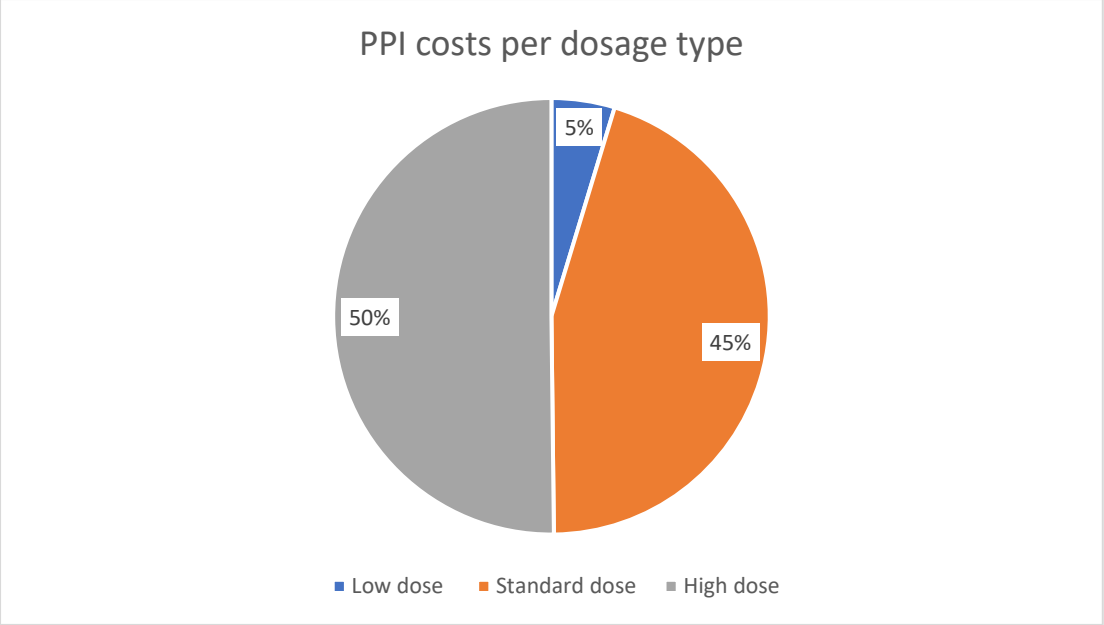

Figure 3: Cost breakdown of dosage type of PPI in 2021

A maximum of two weeks' supply of omeprazole 10 mg and 20 mg, lansoprazole 15 mg and pantoprazole 20 mg are available as OTC formulations in South Africa. The average patient age of OTC PPI claims is 46 years. Table 3 outlines the average cost to the medical schemes for 2021 per OTC claim, per generic entity, based on an average 14-day supply. Omeprazole 20 mg had the highest cost to the medical schemes at an average of R77,42 per OTC claim, followed by lansoprazole 15 mg at an average of R73,00 per OTC claim.

Table 3: Average cost per OTC claim and generic entity in 2021

Generic entity	No. of OTC claims in 2021	Average cost per OTC claim to medical schemes in 2021 (R)
Omeprazole 10mg	238	54,56
Omeprazole 20mg	15 466	77,42
Lansoprazole 15mg	19 562	73,00
Pantoprazole 20mg	2 306	59,25

Discussion

This study aimed to determine the financial implication of acute and OTC PPIs on medical schemes and assess benefit design restrictions implemented by medical schemes as a method of preventing PPI misuse.

The total cost of acute and OTC PPI claims to the four medical schemes amounted to R20 715 453,58. According to the Council for Medical Schemes (CMS), a total of R32.1 billion was paid towards claims by the 75 medical schemes operating in 2021 towards medicines and consumables dispensed by pharmacists and providers other than hospitals. According to the results of this study, the cost of acute and OTC PPI claims for four medical schemes made up 0.065% of the cost (CMS, 2021).

While omeprazole was the most frequently prescribed PPI, dominating with the highest number of claims (34%), esomeprazole was the most expensive PPI, costing the medical schemes a total of R7 881 885,37. It is also noteworthy that high dose esomeprazole formed the largest component (30.08%) of the total cost of acute and OTC PPI claims, as well as 79.02% of the total esomeprazole cost to the medical schemes. These results were also found in a study conducted through similar methods in South Africa in 2011 (Truter, 2014). A study conducted in Ireland also found an increase in PPI expenditure due to the increase in prescribing of esomeprazole (Godman et al., 2010). Another study which compared the efficacy of esomeprazole 20 mg and 40 mg to omeprazole 20 mg in patients with GERD found that both strengths of esomeprazole were significantly more effective than omeprazole, however esomeprazole 40 mg produced the greatest symptom resolution, especially in healing erosive esophagitis (Richter et al., 2001). In contrast, a study which evaluated high-dose versus low-dose esomeprazole in triple therapy for *H. pylori* eradication found that there were no differences in eradication rates between high and low-dose groups (Hsu et al., 2007). It is therefore imperative for prescribers to attain an accurate diagnosis and determine the severity of symptoms so that low-dose regimes can be reasonably recommended to reduce PPI expenditure.

The average patient age for OTC PPI claims was 46 years (SD=17). Pharmacy claims for OTC PPIs cost the schemes a total of R951 006,90, accounting for 4.59% of the cost to the schemes. This was largely comprised of claims for lansoprazole 15 mg and omeprazole 20 mg. The

preference of lansoprazole may be attributed to the fact that a few medical scheme options included in the study make use of an OTC formulary list, where lansoprazole 15 mg is the only OTC PPI generic entity reimbursed by the scheme. Omeprazole may have been favoured as an OTC remedy due to cost-effectiveness, efficiency, and safety. In other studies, omeprazole was also found to be the most dominantly utilized PPI (Truter, 2014). A study conducted in the United States of America by analysis of claims for PPIs submitted to a state employee health plan found that a change in policy to allow the coverage of OTC omeprazole resulted in a 38% net saving to the health plan, despite an overall 6% increase in PPI utilization (West et al., 2006).

About 66% of the total PPI claims were prescribed by general practitioners. Studies have indicated that clinical guidelines and prescribing protocols are not being adhered to, and general practitioners often feel pressured into prescribing certain medicines in order to protect their relationship with patients (Cahir et al., 2012; Pollock & Grime, 2003). A study conducted in the Republic of Ireland concluded that there is a significant opportunity to achieve substantial cost-savings for healthcare funders through stricter implementation of clinical guidelines, generic substitution, and appropriate step-down therapy (Cahir et al., 2012).

The data obtained during this study were solely obtained using generic entities, therefore the cost implication of originators versus generics could not be established. Studies conducted between 2001 and 2007 in a few northern European countries have shown that despite an increase in PPI utilization, a decrease in PPI expenditure was seen through a shift to the prescription of generics (Godman et al., 2010).

The four different medical schemes included in the study include both open schemes (available to all consumers) and restricted schemes (limited to consumers who meet specific qualifying criteria, usually limited to a specific profession or industry) (Josh & Shivani, 2014).These schemes have a variety of product offerings for consumers, known as benefit options. These options differ in their designs to cater for various consumer needs and require approval and registration from the Council for Medical Schemes (CMS) to meet the requirements outlined by the Medical Schemes Act 131 of 1998 (Josh & Shivani, 2014).

Benefit design, or decisions made to determine funding of services and goods (WHO, n.d.), use certain criteria according to clinical recommendations and national protocols as a method of rationing funding for certain medicines and clinical services, and is also dependent on the benefit option selected by the member. These restrictions may be implemented in the form of co-payments, use of closed formulary lists or the implementation of quantity limitations on certain medicines.

In the case of this study, certain benefit options made use of closed OTC formulary lists, therefore only allowing OTC funding of lansoprazole 15 mg. Some options also have a certain Rand value limitation on OTC claims per member per day or month. However, it is interesting to note that with effect from 2023, two out of the four medical schemes included in this study have implemented a quantity limitation of 90 PPIs per year. Similarly, Medicaid® (a health coverage programme in the United States of America for low-income residents) also implemented a quantity limitation on PPIs in 2017, restricting reimbursement to one tablet or capsule a day for a maximum of two months during a twelve-month period (HCA, 2017).

Quantity limitations implemented on PPIs by medical schemes not only save the funder from unnecessary high costs, but also aid in the prevention of misuse of PPIs by their members. PPIs are often prescribed for the relief of symptoms of gastroesophageal reflux disease and heartburn. In most cases, symptom control should be achieved within 8 weeks of treatment, however rebound reflux due to abrupt discontinuation after the initial treatment period often results in the overutilization of PPIs (HCA, 2017).

It is important to note that despite the quantity limitations put into place on PPIs, certain benefit options do cover PPIs for chronic funding for a five-year period, however chronic claims were not included in the data set. In these cases, members need to submit an application to the medical scheme to allow for review of chronic funding and provide a valid gastroscopy report not older than five years confirming the diagnosis of a condition for which long-term PPI treatment is appropriate, i.e. gastroesophageal reflux disease, Zollinger-Ellison syndrome or Barrett's oesophagitis. In these cases, formulary lists are also applicable, preventing overutilization of expensive generic entities such as esomeprazole, as seen in the results of this study. For example, a standard dose of omeprazole cost the schemes an average of R198,94 per claim in 2021, while a standard dose of esomeprazole cost the schemes an

average of R276,84 per claim. In another study, esomeprazole was also found to have the highest cost per prescription at R289,23 (Truter, 2014).

Scheme options which only provide funding for the abovementioned conditions from acute or day-to-day benefits may allow for the annual quantity limitation to be lifted, provided that the appropriate diagnostic report is received, confirming the diagnosis of either gastroesophageal reflux disease, Zollinger-Ellison syndrome, or Barrett's oesophagitis.

Limitations

A few limitations were identified throughout the study. A few of the medical scheme options included in this study do not cover PPIs altogether, and the cost of unpaid claims were excluded from the results, hence the total PPI expenditure could not be determined, but would be much higher than stated in this study. Further research is necessary to determine the true impact of the newly instated annual quantity limitations on the financial implication of PPIs to the medical schemes. The study was only conducted through the analysis of medical scheme claims; hence, the results cannot be extrapolated to reflect the PPI expenditure of the public sector in South Africa.

Conclusion

The study showed that annual PPI expenditure has a large financial impact on medical schemes in South Africa, which can be significantly reduced through stricter implementation of clinical guidelines and protocols by healthcare professionals. PPI therapy should be prescribed only for their registered indications, at the correct dosage and for appropriate treatment duration. Pharmacists also play a vital role in reducing overall PPI expenditure by encouraging the use of cost-effective generics and furnishing appropriate advice for patients seeking symptomatic relief of acid-related disorders. Medical schemes can also use benefit design restrictions, such as annual quantity limitations, to effectively discourage the overutilization of PPIs and significantly reduce the financial implications on the schemes.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

KM was the principal researcher. KM, FO and VB were responsible for the overall study design and conceptualization. KM conducted the data analysis and interpretation with the assistance of VB and FO. KM wrote the article, which was reviewed by all authors.

Funding information

No funding was required for this study.

Data availability statement

The data supporting the findings of this study are available on request from the corresponding author (KM) upon reasonable request.

Disclaimer

The content presented is solely the responsibility of the authors and does not represent the official views of any other organization.

Chapter summary

Chapter five highlighted the costs of acute and OTC PPIs on four medical schemes and reviewed benefit design restrictions as a method of reducing PPI expenditure and preventing their potential misuse.

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Chapter 6: Conclusion

The final chapter summarises the overall findings of the study, describes the significance and limitations, and provides recommendations for future research.

6.1. Summary of findings

The aim of this study was to determine the frequency of acute and over-the-counter (OTC) proton pump inhibitor (PPI) claims submitted by pharmacies to medical schemes in order to assess the possibility of PPI misuse. To achieve this aim, the following objectives were met:

- The available PPIs and their indications for safe use were reviewed.
- The frequency of PPI claims per patient was analyzed and the results were compared. to safe indications for use.
- The costs of acute and OTC PPI claims on medical schemes were determined and reviewed.
- The possibility of implementing different benefit design restrictions by medical schemes were reviewed as a method of preventing PPI misuse and reducing the overall coststo the scheme.

Conclusions were drawn and summarized based on each objective.

- Five different PPI generic entities are registered for use in South Africa, with three being available for OTC usage (lansoprazole 15 mg, pantoprazole 20 mg and omeprazole 10 mg and 20 mg). Clinical guidelines recommend the use of OTC PPIs for most gastric acid-related disorders for a maximum of three courses per year, with each course lasting 14 days. Omeprazole was the most frequently utilized PPI, accounting for 34% of the claims, perhaps due to cost-effectiveness. The average number of PPI claims per patient for the twelve month period was 8 (SD=3.94), indicating an average treatment duration of 240 days. PPIs are being used for longer durations than recommended and for unclear indications, leading to overutilization and misuse.
- A total of 268 537 acute and OTC PPI claims were submitted by 81 566 patients to four different medical schemes in 2021. There was a significant relationship established between patient age and frequency of PPI claims, with higher patient age being

associated with more frequent PPI usage. An average of 5 claims per patient were submitted for patients over the age of 60 years. Acute claims made up 86.01% of the total claims, indicating that the majority of PPIs claimed were prescribed by a medical practitioner, more than half of which were prescribed by a general practitioner (66%). Prescribers need to re-assess patient needs and consider deprescribing of PPIs in patients who no longer have a clear rationale for PPI therapy, in order to prevent the risk of long-term adverse effects and masking of more serious underlying conditions.

- At least 66.52% of the claims were for a quantity of thirty tablets or capsules, with an average of three claims per patient being submitted consecutively, indicating an average duration of twelve weeks of PPI therapy, significantly longer than the usual recommended treatment duration of four to eight weeks for the short-term management of acid-related disorders. Close to half of the claims (43.74%) were submitted by patients over the age of 60 years, strongly suggesting potential misuse and overutilization of PPIs in the elderly population. The incidence of gastrointestinal-related disorders increases with age, especially as a result of polypharmacy, however clinical guidelines for the safe use of PPIs should be strictly adhered to. Polypharmacy in the elderly is of growing concern, and extended duration of PPI therapy may pose a significant risk of osteoporosis, gastrointestinal infections and masking of early symptoms of gastric cancers.
- Acute and OTC PPIs cost the four medical schemes a total of R20 715 453,58 for the year. Esomeprazole was the third most frequently claimed PPI, but accounted for the largest portion of the costs funded by the schemes (R7 881 885,37) followed by omeprazole (R6 356 452,24). High dose esomeprazole accounted for 30.08% of the total financial implication to the scheme. Factors contributing to the preference of high-dose esomeprazole may include faster improvement in clinical signs and symptoms and possible treatment failure with low-dose PPIs. OTC PPIs cost the medical schemes R951 006,90, of which lansoprazole 15 mg accounted for more than half the cost (R502 737,10). High-dose PPIs should be reserved for the treatment of severe conditions according to their registered indications, and the use of cost-effective alternative therapies such as H_2-receptor antagonists and antacids should be encouraged as an alternative to PPI therapy where appropriate.

- Two of the medical schemes included in the study implemented benefit design restrictions to prevent the overutilization of PPIs by their members through annual quantity limitations. This allows members to claim for a maximum reimbursable quantity on PPIs of 90 tablets or capsules per year. Some medical schemes also utilize an acute and OTC formulary list, which only pays for certain generic entities in order to encourage the use of cost-effective products, thereby reducing PPI expenditure. Through the implementation of formulary lists, the use of more cost-effective generics can be encouraged to lessen the financial burden on medical schemes. This policy may also reduce prescribing of high-dose PPIs for minor conditions.

6.2. Significance of the study

This study highlights the prevalence of PPI misuse, and the impact thereof on medical schemes in South Africa. Despite PPIs being safe and highly efficacious drugs for the management of acid-related disorders, it is crucial that they are prescribed only when necessary and strictly according to their registered indications and treatment duration. The study also emphasizes the importance of the pharmacist's role in reducing OTC PPI expenditure by identifying possible misusers of PPIs, counselling patients on healthy lifestyle measures to assist in the prevention of acid-related disorders and encouraging the use of cost-effective generics and alternatives to PPI therapy.

6.3. Strengths

The findings of this study contribute to the existing literature and fill in any gaps in previous studies on the misuse of PPIs. The findings of the study will also assist in making prescribers more aware of the current extent of PPI overutilization, especially in the elderly population, and encourage more mindful prescribing of PPIs according to clinical guidelines for appropriate indications.

6.4. Limitations

The study was restricted to four medical schemes, hence the trends identified in PPI usage cannot be extrapolated to reflect prescribing of PPIs in the public sector. The results can only be generalised to medical schemes with the same patient mix and formulary designs. Time constraints also prevented claims from being analyzed over a longer period of time to possibly identify changes in PPI usage pre- and post-COVID. The indications for PPI usage were also unknown, hence an accurate comparison of PPI usage and their registered indications could not be made. An accurate assessment of the financial impact to the four medical schemes could not be made as the total medicine costs to the medical schemes in 2021 could not be obtained.

6.5. Recommendations

- This study was restricted to four medical scheme claims. Further studies should analyze cash purchases of acute and OTC PPIs and the prescribing of PPIs in hospitals in public and private sectors in order to gain a broader understanding of the overall PPI usage and its financial implications in South Africa.
- Further research should be conducted to investigate the long-term adverse effects of PPIs, as many of the current studies are inconclusive or conflicting with other studies.
- Healthcare professionals should strictly adhere to national PPI prescribing guidelines. Ongoing acid-related symptoms which remain unresolved after the recommended duration of PPI treatment should be referred for further appropriate investigative procedures.
- Further studies should investigate the effect of benefit design limitations on PPI expenditure, and medical schemes should investigate additional measures to reduce the financial impact of PPI expenditure on the schemes and assist with discouraging inappropriate prescribing and misuse of these drugs.

Chapter summary

The final chapter summarized the findings of this study, identified gaps in current studies and provided recommendations for future studies.

Annexure 1: BREC approval letter

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

08 August 2022

Miss Kajal Mohanlal (214504633)
School of Health Sciences
Westville

Dear Miss Mohanlal,

Protocol reference number: BREC/00004235/2022
Project title: Overview of proton pump inhibitor use: A medical scheme perspective
Degree: Masters

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 08 August 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 08 August 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

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

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

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

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 September 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Annexure 2: Gatekeeper permission letter

mediscor pbm
Pharmaceutical Benefit Management

19 May 2022

Miss Kajal Mohanlal (9507130088086)

School of Health Sciences

College of Health Sciences

Westville Campus

UKZN

Email: mohanlalkajal00@gmail.com

Dear Miss Mohanlal

RE: PERMISSION TO CONDUCT RESEARCH

"Gatekeeper's permission" is hereby granted for you to conduct research using data generated by Mediscor PBM, towards your postgraduate studies, provided ethical clearance has been obtained.

We note the title of your research project is:

"Overview of proton pump inhibitor use: A medical scheme perspective."

Identity numbers, email addresses and other personal information of individuals are not a matter of public record and are protected according to Section 14 of the South African Constitution, as well as the PAIA and POPI Act. Data collected must be treated with due confidentiality and anonymity.

Yours sincerely,

[redacted]

Francois Venter

Chief Operating Officer

Annexure 3: Data summary

Table 1: Member age

	N	Mean	SD	Min	Max
Member age (years)	268537	55.8444	17.39807	0	102

Table 2: Frequency of claims per month

Month	Frequency	Percentage (%)	Cumulative
1	28 598	10.65	10.65
2	25 881	9.64	20.29
3	29 142	10.85	31.14
4	25 410	9.46	40.60
5	25 082	9.34	49.94
6	23 263	8.66	58.60
7	22 097	8.23	66.83
8	20 942	7.80	74.63
9	18 890	7.03	81.67
10	17 362	6.47	88.13
11	15 974	5.95	94.08
12	15 896	5.92	100.00
Total	268 537	100.00	

Table 3: Claims per age group

Age group (years)	Frequency	Percentage	Cumulative
0-2	1 261	0.47	0.47
3-12	1 723	0.64	1.11
13-39	46 500	17.32	18.43
40-59	101 601	37.84	56.26
> 60	117 452	43.74	100.00
Total	268 537	100.00	

Table 4: Claims per sex

Sex	Frequency	Percentage	Cumulative
Female	157 566	58.68	58.68
Male	110 971	41.32	100.00
Total	268 537	100.00	

Table 5: Claims per generic entity

Generic entity	Frequency	Percentage
Esomeprazole magnesium for delayed release susp pack 2.5 mg	420	0.16
Esomeprazole magnesium for delayed release susp packet 5 mg	632	0.24
Esomeprazole magnesium for delayed release susp packet 10 mg	641	0.24
Esomeprazole magnesium tab delayed release 20 mg	15 879	5.91
Esomeprazole magnesium tab delayed release 40 mg	46 281	17.23

Lansoprazole cap delayed release 15 mg	24 435	9.10
Lansoprazole cap delayed release 30 mg	21 037	7.83
Omeprazole magnesium for inj 40 mg	10	0.00
Omeprazole magnesium tab ER 10 mg	1 156	0.43
Omeprazole magnesium tab ER 20 mg	82 930	30.88
Omeprazole magnesium tab ER 40 mg	6 754	2.52
Pantoprazole sodium EC tab 20 mg (base equiv)	19 832	7.39
Pantoprazole sodium EC tab 40 mg (base equiv)	45 732	17.03
Pantoprazole sodium for IV soln 40 mg (base equiv)	707	0.26
Rabeprazole sodium EC tab 10 mg	439	0.16
Rabeprazole sodium EC tab 20 mg	1 375	0.51
Total	268 537	100.00

Table 6: Claims per benefit category

Benefit category	Frequency	Percentage	Cumulative
Acute	230 965	86.01	86.01
OTC	37 572	13.99	100.00
Total	268 537	100.00	

Table 7: Frequency of claims per quantity

Quantity	Frequency	Percentage	Cumulative
1	764	0.28	0.28
2	294	0.11	0.39
3	179	0.07	0.46
4	63	0.02	0.48
5	683	0.25	0.74
6	314	0.12	0.86
7	3 409	1.27	2.12
8	116	0.04	2.17
9	16	0.01	2.17
10	3 926	1.46	3.64
11	13	0.00	3.64
12	385	0.14	3.78
13	31	0.01	3.80
14	44 209	16.46	20.26
15	1 751	0.65	20.91
16	58	0.02	20.93
17	12	0.00	20.94
18	127	0.05	20.98
19	15	0.01	20.99
20	972	0.36	21.35
21	304	0.11	21.46
22	15	0.01	21.47
23	570	0.21	21.68
24	30	0.01	21.69
25	26	0.01	21.70
26	31	0.01	21.72
27	16	0.01	21.72
28	25 970	9.67	31.39
29	16	0.01	31.40

30	178 628	66.52	97.92
31	13	0.00	97.92
32	6	0.00	97.92
33	1	0.00	97.92
34	7	0.00	97.93
35	31	0.01	97.94
36	10	0.00	97.94
37	5	0.00	97.94
38	3	0.00	97.95
39	2	0.00	97.95
40	75	0.03	97.97
41	1	0.00	97.97
42	77	0.03	98.00
44	17	0.01	98.01
45	94	0.04	98.04
46	48	0.02	98.06
47	2	0.00	98.06
48	3	0.00	98.06
50	10	0.00	98.07
52	4	0.00	98.07
55	1	0.00	98.07
56	488	0.18	98.25
58	3	0.00	98.25
59	2	0.00	98.25
60	4 669	1.74	99.99
90	15	0.01	100.00
120	3	0.00	100.00
180	4	0.00	100.00
Total	268 537	100.00	

Table 8: Claims per provider type

Provider type	Frequency	Percentage	Cumulative
General medical practice	12 444	4.63	4.63
Group practice	32	0.01	4.65
Group practices/hospitals	4	0.00	4.65
Pharmacies	255 850	95.28	99.92
Phy/im/rheu/neph/diab/end	1	0.00	99.92
Private hospital (a tarif)	16	0.01	99.93
Private hospital (b tarif)	71	0.03	99.96
Radiation oncology	2	0.00	99.96
Registered nurses	1	0.00	99.96
Rehab hospital (acute)	1	0.00	99.96
Specialist family medicine	108	0.04	100.00
Sub-acute facilities	2	0.00	100.00
Surgery	5	0.00	100.00
Total	268 537	100.00	

Table 9: Claims per prescriber type

Prescriber type	Frequency	Percentage	Cumulative
Accredited blood couriers	1	0.00	0.00
Ambulance services	3	0.00	0.00
Anaesthetists	315	0.12	0.12
Approved day clinics	49	0.02	0.14
Biokinetics	1	0.00	0.14
Cardio thoracic surgery	116	0.04	0.18
Cardiology	468	0.17	0.35
Chiropractors	3	0.00	0.36
Clinical haemotology	124	0.05	0.40
Clinical pharmacology	6	0.00	0.40

Clinical services	3	0.00	0.41
Dental therapy	5	0.00	0.41
Dermatology	324	0.12	0.53
Diagnostic radiology	60	0.02	0.55
Dieticians	10	0.00	0.55
Emergency medicine	65	0.02	0.58
Gastroenterology	13	0.00	0.58
General dental practice	652	0.24	0.83
General medical practice	177 239	66.00	66.83
Group practice	821	0.31	67.13
Group practices/hospitals	36	0.01	67.15
Hospices	3	0.00	67.15
Maxillo-facial & oral surg	58	0.02	67.17
Medical oncology	10	0.00	67.17
Mental health institution	3	0.00	67.17
Neurology	1 115	0.42	67.59
Neurosurgery	325	0.12	67.71
Nuclear medicine	16	0.01	67.72
Obstetrics & gynaecology	1 802	0.67	68.39
Occupational medicine	2	0.00	68.39
Ophthalmology	733	0.27	68.66
Optometrists	4	0.00	68.66
Orthodontics	13	0.00	68.67
Orthopaedics	964	0.36	69.03
Otorhinolaryngology	1 735	0.65	69.67
Paediatric surgery	6	0.00	69.67
Paediatrics	1 586	0.59	70.27
Pathology	66	0.02	70.29
Periodontics	20	0.01	70.30
Pharmacies	37 637	14.02	84.31
Pharmacotherapist	332	0.12	84.44

Phy/im/rheu/neph/diab/end	26 502	9.87	94.31
Physical medicine	16	0.01	94.31
Physiotherapists	5	0.00	94.31
Plastic & recon surgery	78	0.03	94.34
Podiatry	1	0.00	94.34
Primary care drug therapist	8	0.00	94.35
Private hospital (a tarif)	57	0.02	94.37
Private hospital (b tarif)	205	0.08	94.44
Prosthodontics	2	0.00	94.44
Provincial hospital	1 232	0.46	94.90
Psychiatry	2 626	0.98	95.88
Public health medicine	6	0.00	95.88
Pulmonology	37	0.01	95.90
Radiation oncology	991	0.37	96.27
Radiography	5	0.00	96.27
Registered nurses	37	0.01	96.28
Rehab hospital (acute)	1	0.00	96.28
Rheumatology	664	0.25	96.53
Specialist family medicine	1 993	0.74	97.27
Sub-acute facilities	6	0.00	97.27
Surgery	6 518	2.43	99.70
Urology	803	0.30	100.00
Total	**268 537**	**100.00**	

Annexure 4: Submission guidelines for Inquiry: Journal of health care organization, provision and financing

1. Open Access

Inquiry is an open access, peer-reviewed journal. Each article accepted by peer review is made freely available online immediately upon publication, is published under a Creative Commons license and will be hosted online in perpetuity. Publication costs of the journal are covered by the collection of article processing charges which are paid by the funder, institution or author of each manuscript upon acceptance. There is no charge for submitting a paper to the journal.

2. Article processing charge (APC)

If, after peer review, your manuscript is accepted for publication, a one-time article processing charge (APC) is payable. This APC covers the cost of publication and ensures that your article will be freely available online in perpetuity under a Creative Commons licence. The APC for this journal is 2200 USD.

3. What do we publish?

Every effort should be made by the author to ensure that the main document file contains no clues as to the author identity of the author.

On the first page should be the abstract (a maximum of 250 words) and 4-5 keywords. All tables should be placed at the end of the file and numbered in the order they appear in the text. We strongly encourage the appropriate use of bar charts and line graphs to illustrate key findings. Figures should be placed in individual text files, separate from the main document file.

Article types published by Inquiry are given below, with limits on words and in-text tables given in brackets. Word limits include tables, but not abstracts, key words, or references.

- Original Research (5000 words, 3 tables)
- Reviews, including Systematic Reviews (5000 words, 3 tables)

- Case Studies (2000 words, 3 tables)
- Policy Briefs (1000 words, 1 table)
- Editorials (3000 words, 3 tables)
- Comment (1000 words) – Intended for responses to published papers or responses to other comments. Article Processing Charge (APC) will be waived.

All article types require a structured abstract except commentaries, which include a summary. Citations should be numbered in AMA style. A citation program such as EndNote should be used.

4. Editorial policies

4.1 Peer review policy

Following a preliminary triage to eliminate submissions unsuitable for Inquiry, all papers are sent out for review.

Please include a cover letter in your submission. To help the Editor in his preliminary evaluation, please indicate in this letter why you think the paper is suitable for publication. The journal's policy is to have manuscripts reviewed by two expert reviewers. Inquiry utilizes a double anonymized peer review process in which the reviewer and author's names and information are withheld from the other. All manuscripts are reviewed as rapidly as possible, while maintaining rigor. Peer review is managed by the SAGE Managing Editor who assigns each submitted manuscript to appropriate reviewers and, with the input of the Editorial Board, and comments and recommendations of the reviewers, makes decisions on the eligibility of the article for publication.

4.2 Authorship

Papers should only be submitted for consideration once consent is given by all contributing authors.

Those submitting papers should carefully check that all those whose work contributed to the paper are acknowledged as contributing authors. The list of authors should include all those who can legitimately claim authorship. This is all those who:

(i) Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,

(ii) Drafted the article or revised it critically for important intellectual content,
(iii) Approved the version to be published,

(iv) Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.
When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship, although all contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section.

4.3 Acknowledgements

All contributors who do not meet the criteria for authorship should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, or a department chair who provided only general support.

4.3.1 Third party submissions

Where an individual who is not listed as an author submits a manuscript on behalf of the author(s), a statement must be included in the Acknowledgements section of the manuscript and in the accompanying cover letter. The statements must:

- Disclose this type of editorial assistance – including the individual's name, company and level of input
- Identify any entities that paid for this assistance

- Confirm that the listed authors have authorized the submission of their manuscript via third party and approved any statements or declarations, e.g. conflicting interests, funding, etc.

Where appropriate, SAGE reserves the right to deny consideration to manuscripts submitted by a third party rather than by the authors themselves.

4.3.2 Writing assistance

Individuals who provided writing assistance, e.g. from a specialist communications company, do not qualify as authors and so should be included in the Acknowledgements section. Authors must disclose any writing assistance – including the individual's name, company and level of input – and identify the entity that paid for this assistance").

It is not necessary to disclose use of language polishing services.

Please supply any personal acknowledgements separately to the main text to facilitate anonymous peer review.

4.4 Funding

Inquiry requires all authors to acknowledge their funding in a consistent fashion under a separate heading. Please visit the Funding Acknowledgements page on the SAGE Journal Author Gateway to confirm the format of the acknowledgment text in the event of funding, or state that: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

4.5 Declaration of conflicting interests

It is the policy of Inquiry to require a declaration of conflicting interests from all authors, enabling a statement to be carried within the paginated pages of all published articles.

Please ensure that a 'Declaration of Conflicting Interests' statement is included at the end of your manuscript, after any acknowledgements and prior to the references. If no conflict exists, please state that 'The Author(s) declare(s) that there is no conflict of interest'.

For guidance on conflict of interest statements, please see the ICMJE recommendations.

4.6 Research ethics and patient consent

Medical research involving human subjects must be conducted according to the World Medical Association Declaration of Helsinki.

Submitted manuscripts should conform to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, and all papers reporting animal and/or human studies must state in the methods section that the relevant Ethics Committee or Institutional Review Board provided (or waived) approval. Please ensure that you have provided the full name and institution of the review committee, in addition to the approval number.

For research articles, authors are also required to state in the methods section whether participants provided informed consent and whether the consent was written or verbal.

Information on informed consent to report individual cases or case series should be included in the manuscript text. A statement is required regarding whether written informed consent for patient information and images to be published was provided by the patient(s) or a legally authorized representative. Please do not submit the patient's actual written informed consent with your article, as this in itself breaches the patient's confidentiality. The Journal requests that you confirm to us, in writing, that you have obtained written informed consent but the written consent itself should be held by the authors/investigators themselves, for example in a patient's hospital record. The confirmatory letter may be uploaded with your submission as a separate file.

Please also refer to the ICMJE Recommendations for the Protection of Research Participants.

All research involving animals submitted for publication must be approved by an ethics committee with oversight of the facility in which the studies were conducted. The Journal has adopted the ARRIVE guidelines.

4.7 Clinical trials

Inquiry conforms to the ICMJE requirement that clinical trials are registered in a WHO-approved public trials registry at or before the time of first patient enrolment as a condition of consideration for publication. The trial registry name and URL, and registration number must be included at the end of the abstract.

4.8 Reporting guidelines

The relevant EQUATOR Network reporting guidelines should be followed depending on the type of study. For example, all randomized controlled trials submitted for publication should include a completed Consolidated Standards of Reporting Trials (CONSORT) flow chart as a cited figure, and a completed CONSORT checklist as a supplementary file.

Other resources can be found at NLM's Research Reporting Guidelines and Initiatives.

4.9 Data

At SAGE we are committed to facilitating openness, transparency and reproducibility of research. *Inquiry* requests all authors to share their research data in a suitable public repository as a condition of publication. This is subject to ethical considerations and in such cases the journal editor may grant an exception and authors should contact the Editorial Office at umair.shafique@sagepub.com. Authors are also required to include a data accessibility statement in their manuscript file and to follow data citation principles. For more information please visit the SAGE Author Gateway, which includes information about SAGE's partnership with the data repository Figshare.

5. Publishing policies

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6. Preparing your manuscript

6.1 Word processing formats

Preferred formats for the text and tables of your manuscript are Word DOC, RTF, XLS. LaTeX files are also accepted. The text should be double-spaced throughout and with a minimum of 3cm for left and right hand margins and 5cm at head and foot. Text should be standard 10 or 12 point. Word and (La)Tex templates are available on the Manuscript Submission Guidelines page of our Author Gateway.

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6.4 Journal layout

Inquiry conforms to the AMA style.

6.5 Reference style

Inquiry adheres to the reference style specified in the AMA Manual of Style 11th Edition.

6.6 English language editing services

Authors seeking assistance with English language editing, translation, or figure and manuscript formatting to fit the journal's specifications should consider using SAGE Language

Services. Visit SAGE Language Services on our Journal Author Gateway for further information.

7. Submitting your manuscript

7.1 How to submit your manuscript

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IMPORTANT: Please check whether you already have an account in the system before trying to create a new one. If you have reviewed or authored for the journal in the past year it is likely that you will have had an account created.

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Prior to submitting, you may consider running your manuscript through the Paperpal Preflight service, which instantly checks your manuscript and helps you address the most common errors and omissions.

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You will be asked to provide contact details and academic affiliations for all co-authors via the

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Annexure 5: Confirmation of manuscript submission to INQUIRY: The Journal of Health Care Organization, Provision and Financing.

Submission Confirmation

Print

Thank you for your submission

Submitted to	INQUIRY
Manuscript ID	INQ-23-0469
Title	An overview of proton pump inhibitor usage by members of medical schemes in South Africa
Authors	Mohanlal, Kajal Bangalee, Varsha Oosthuizen, Frasia
Date Submitted	19-Jun-2023

Submission Confirmation

Print

Thank you for your submission

Submitted to	INQUIRY
Manuscript ID	INQ-23-0470
Title	The financial implication of acute and over-the-counter proton pump inhibitor usage on medical schemes.
Authors	Mohanlal, Kajal Oosthuizen, Frasia Bangalee, Varsha
Date Submitted	19-Jun-2023