Title
Education to Reduce Inappropriate Use of Proton Pump Inhibitors in Patients with Cirrhosis

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Education to Reduce Inappropriate Use of Proton Pump Inhibitors in Patients with Cirrhosis

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Nursing Practice

by

Juvelyn Junio Palomique

2021

ABSTRACT OF THE DISSERTATION

Education to Reduce Inappropriate Use of Proton Pump Inhibitors in Patients with Cirrhosis

by

Juvelyn Junio Palomique

Doctor of Nursing Practice

University of California, Los Angeles, 2021

Professor Mary-Lynn Brecht, Co-Chair

Professor Paul Macey, Co-Chair

Background: Inappropriate use of proton pump inhibitors (PPI) is common in patients with cirrhosis. PPIs are associated with deleterious effects in cirrhosis including increased risk for hepatic encephalopathy, spontaneous bacterial peritonitis, and liver-related mortality. **Objectives**: The aim was to decrease the incidence of low-value, non-guideline supported prescription of PPIs in the inpatient setting with a PPI Clinician Update education and a PPI stewardship by Hepatology. **Methods:** The study was implemented in a single inpatient transplant center. Key medical staff were identified to receive a PPI Clinician Update educational session, including Hospitalist, Gastroenterology fellows, Hepatology and Liver transplant

advanced practice provider (APP). Patient data providing incidence of inappropriate PPI prescription was evaluated under a non-equivalent group pre-posttest design. The study used a one group pre-posttest design for assessing change in provider knowledge levels. A designated hepatology APP steward reviewed all PPI prescription appropriateness. Inappropriate PPI prescription was discontinued by the Hepatology APP who provided constructive feedback to the providers. The primary outcome measure was the incidence of inappropriate PPI prescription before and after the education session which were compared using a chi square test. Secondary outcome was percentage of correct responses (from a total of 10 questions), with before- and after-education measures compared using a paired t-test. **Results:** Twenty-six providers completed the educational session and pre-posttest. Lack of knowledge regarding outpatient PPI indication was reported as the main barrier to verifying PPI prescription. There was a statistically significant 20% increase in knowledge ($p < .001$) one month after receiving the educational intervention. There was a decrease in the incidence of inappropriate PPI use from 52% (23/44) to 25% (11/44) ($p = .009$) one month after receiving the educational intervention. The most common reason for inappropriate PPI prescription was continuation of the patient's home medication without verifying the indication. The posttest survey showed that 46% of clinicians strongly agreed that their practice changed after the educational intervention and constructive feedback. **Conclusion:** The most common reason for inappropriate PPI prescription was due to a continuation of a home medication without verifying the indication. A multifaceted approach including an educational intervention and hepatology stewardship was effective in increasing knowledge and decreasing the inappropriate PPI prescriptions in the inpatient setting.

The dissertation of Juvelyn Junio Palomique is approved.

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2021

DEDICATION

This dissertation is dedicated to my darling Stephen John Harrison, who has been a constant companion, empowering me to push through to the finish line despite multiple challenges along the way. You have been my inspiration and a source of strength when I lacked motivation. To my parents, you have set an example of excellence. Lastly, I dedicate this dissertation to Dr. Nancy Jo Bush and Soo Kwon. Without your guidance and unwavering support, I would not be where I am today. I am truly thankful for your kindness, patience, and expertise. To my dearest Michelle Panlilio and Jackson Huang, you have made the entire DNP experience manageable and fun during a chaotic pandemic. Thank for being an every present support system during a time of uncertainty and creating a team work environment, pushing each other to new levels of excellence.

TABLE OF CONTENTS

List of Figures and Tables

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4. Sun, N., Lee, Y. T., Kim, M., Wang, J. J., Zhang, C., Teng, P. C., Qi, D., Zhang, R. Y., Tran, B. V., Lee, Y. T., Ye., J., **Palomique, J.**, Nissen, N. N., Han, S. B., Sadeghi, S., Finn, R. S., Saab, S., Busuttil, R. W., Posadas, E. M., Liang, L., Pei, R., Yang, J. D., You, S., Agopian, V. G., Tseng, H. R., & Zhu, Y. (2021). Covalent chemistry-mediated multimarker purification of circulating tumor cells enables noninvasive detection of molecular signatures of hepatocellular carcinoma. *Advanced Materials Technologies*, 1-11. https://doi.org/10.1002/admt.202001056

CHAPTER ONE: INTRODUCTION

The focus of the Doctor of Nursing Practice (DNP) quality improvement (QI) project was to reduce unnecessary, low-value proton pump inhibitor (PPI) prescription in patients with cirrhosis. A multi-strategy intervention was utilized and included an educational session, deprescribing algorithm, and hepatology advance practice provider (APP) stewardship. The term low-value prescription was defined as lacking long-term guideline-based indication. It is estimated that 15 million adults in the United States have a PPI prescription (Al-Aly et al., 2020). One in eight older adults, age 65 years or older, had a PPI prescription; however, one-third of PPI prescriptions were low-value (Mafi et al., 2019). De Roza et al. (2019) suggested that up to two-thirds of hospitalized patients with cirrhosis had a PPI prescription without a clear justification for its use. Unfortunately, the long-term safety profile of PPIs was controversial because long-term use has not been tested or approved by the Federal Food and Drug Administration (FDA). Adverse side effects associated with PPIs included increased risk of *Clostridium difficile* and COVID-19 infection, osteoporosis, nephrotoxicity and other complications associated with polypharmacy and drug-drug interactions (Almario et al., 2020; Ren et al., 2019; Tandun et al., 2019). Patients with cirrhosis were particularly vulnerable to the adverse effects of PPI use. Review of literature revealed patients with cirrhosis who used PPI had increased risk of hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP), increased mortality and hospital readmission (Bajaj et al., 2018; Dam et al., 2016; De Roza et al., 2019; Hung et al., 2018; Tantai et al., 2019).

Problem Statement, Objective, and PICOT Question

Medication review for patients with cirrhosis suggested there was over-prescription of PPI within the institution of study, despite a built-in electronic medical record (EMR) indication

verification (see Appendix A). The objective of the DNP project was to increase adherence to guideline-based indication for PPI prescription after implementation of the following: 1) an educational session targeting prescribing clinicians, 2) incorporating an evidence-based deprescribing PPI algorithm, and 3) implementation of hepatology APP stewardship with subsequent healthcare provider feedback. The clinical PICOT question was as follows: In hospitalized adult patients with cirrhosis (P), did an educational intervention combined with a hepatology APP supervision and feedback (I), compared to current practice of hospitalist review alone (C), lead to an increased clinician knowledge and decreased incidence of low-value PPI prescription (O), within one month of implementation (T)?

CHAPTER TWO: THEORETICAL FRAMEWORK

The first step towards implementation of evidence-based practice (EBP) was the evaluation of a guiding scientific underpinning, designated by the American Association of College of Nurses DNP Essential (AACN, 2006). The scientific underpinnings of nursing practice integrates the biologic, physiologic, psychologic and nursing sciences that were essential to the scientific process in order to understand, address, and subsequently evaluate an EBP intervention (Gordon, 2018). The guiding theoretical framework for the QI project was Avedis Donabedian's quality assurance model. The framework included three concepts: structure, process, and outcome (Anderson, 2018; Upenieks & Abelew, 2006). Structure was defined as the stable characteristics of an organization such as how health care services were provided: infrastructure, finances, and resources (Anderson, 2018). Process was the mechanism underlying the organizational activities (Upenieks & Abelew, 2006). Outcome represented the impact on the patient including mortality, length of stay, adverse incidents, patient satisfaction, and cost of care (Anderson, 2018; Upenieks & Abelew, 2006). The relationship between these three concepts was

simple and linear. In order to create the most efficient and effective process to achieve the most beneficial patient health outcome, a good structure needed to support the development of a good process which in turn resulted in good outcomes (Upenieks & Abelew, 2006).

The prior medication review practice was fragmented and lacked comprehensive review as consultants focused primarily on their respective organ system. The hepatology APP improved the existing medication review infrastructure and served as a hospitalist resource. Hepatology provided guidance to address the comprehensive and specialized health care needs of patients with cirrhosis. The APP served as the care coordinator between multiple teams and played a pivotal position to implement a process for reviewing PPI prescription and an evidence-based algorithm to guide deprescribing an inappropriate medication. The improved infrastructure provided by hepatology led to the implementation of a process for the goal of improving adherence to guideline-based indication for PPI prescription.

CHAPTER THREE: REVIEW OF LITERATURE

Clinical Indication for Deprescribing PPI

The articles were derived using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) method as depicted in Appendix B. Using PubMed and CINAHL database, the following key terms were used to yield a total of 683 articles: cirrhosis and PPI; PPI and hepatic decompensation. Full articles published within the last five years were included. Eligible articles were narrowed to cirrhosis-related complications focusing on HE, SBP, mortality, and re-admission rate.

A quantitative readmission study performed by Bajaj et al. (2018) demonstrated that PPI use was associated with a higher readmission rate at 30-days and 90-days, $p = 0.002$, $p = 0.008$ respectively. The study examined the effect of PPI on gut microbiome by performing stool

studies. The authors found that PPI use led to increased oral-origin microbial taxa in both cirrhotic patients and characteristic-matched healthy individuals. Furthermore, PPI use was associated with lower, potentially beneficial, autochthonous taxa (Bajaj et al., 2018). The gut microbiome mismatch, higher oral-origin microbial taxa with lower autochthonous taxa, was thought to be responsible for precipitating hepatic decompensation.

According to Horvath et al. (2019), PPI use led to gut dysbiosis because the medication changed the composition of the gut flora. There was a loss of diversity in the distal intestine, small intestinal bacterial overgrowth, and increased bacterial load in gastric fluid. As a consequence, there was increased inflammation and gut permeability, leading to bacterial translocation and endotoxemia. The observational study performed by Horvath et al. (2019) suggested that the presence of gut biomarkers can predict the severity of the dysbiosis and serve as independent predictors for liver-related three-year mortality.

The quantitative retrospective database study performed by Hung et al. (2018) compared hospitalized patients with HE without gastrointestinal bleeding who were given PPI to a non-PPI group. The authors revealed increased short-term and long-term mortality after hazard Cox regression model analysis adjusted for age, gender, comorbid conditions, and Model for End-Stage Liver Disease (MELD) score. The strength of the study was a large sample size, comparing 1004 cirrhotic patients with PPIs to 4016 cirrhotic patients without PPIs. The above findings were supported by the retrospective database study performed by De Roza et al. (2019), which showed PPI use led to a higher incidence of hospitalization for hepatic decompensation [adjusted Risk Ratio [aRR] = 1.61, (1.30-2.11); $p < 0.001$]. Long term PPI use was associated with higher mortality [adjusted Hazard Ratio [aHR] 2.10 (CI 1.20- 3.67); $p = 0.009$], and it appeared that the effect was dose dependent. Increased continuous dose dependent days (cDDD

> 90) was associated with higher mortality [aHR = 2.27, (1.10-5.14); p = 0.038] compared to non-users.

The study performed by Tantai et al. (2019) was a meta-analysis examining adult patients with compensated or decompensated cirrhosis. The study revealed that PPI use was associated with a 2.08- fold higher risk of HE progression. Dam et al. (2016) examined the association between PPI and the risk of developing HE or SBP in patients with cirrhosis and ascites. The researchers used existing data from three multinational satavaptan randomized control trials (RCT) conducted between July 2006 and December 2008. The hazard ratio of HE for PPI users was 1.36 (95% CI, 1.01 - 1.84). The hazard ratio for overt HE was higher at 1.88 (95% CI, 1.21 - 1.91) whereas the hazard ratio for SBP was 1.72 (95% CI, 1.10 - 2.69) (Dam et al., 2016). The data suggested PPI use was associated with increased risk of developing or having a severe form, of HE and SBP in patients with ascites. The longitudinal study showed that 52% of cirrhotic patients with ascites used PPI at some point during the one-year follow-up giving evidence regarding its ubiquitous use (Dam et al., 2016).

The current body of literature suggests medical providers needed to exercise increased caution in prescribing PPI in patients with cirrhosis (Bajaj et al., 2018; Dam et al., 2016; De Roza et al., 2019; Hung et al., 2018; Tantai et al., 2019). Long-term PPI use is not benign. Clinicians should weigh the risk-benefit ratio for PPI use and should use the lowest effective dose for the shortest effective treatment duration (Bajaj et al., 2018; Dam et al., 2016; De Roza et al., 2019; Hung et al., 2018; Tantai et al., 2019).

Health Care Provider: Education and Behavioral Change

Over-prescription of PPI in the ambulatory and hospital settings ranged from 20 to 80% (Walker et al., 2019). The goal of the QI project was to change clinician prescribing behaviors.

In a systematic review by Tomasone et al. (2020), they examined strategies to translate guidelines into clinical practice. The authors examined 33 studies and found the most utilized intervention was education followed by guideline compliance feedback and reminder system. According to Tomasone et al. (2020), education in addition to an organizational process, such as an implementation team, resulted in a significant positive behavioral change compared to education alone.

Methods to Deprescribe PPI

The following articles were derived using the PRISMA method as depicted in Appendix C. Using PubMed and CINAHL database, the following key terms were used to yield a total of 175 articles: PPI, prescribing and intervention; deprescribe and PPI; and PPI and educational intervention. The search was further narrowed to full articles within the last five years, excluding non-research articles, patient-centered intervention, and non-PPI focused.

The longitudinal quasi-experimental study by Del Giorno et al. (2018) partnered with five teaching hospitals to create a multifaceted strategy in decreasing the incidence of in-hospital PPI prescription. The internal medicine clinicians received educational interventions and a continuous transparent monitoring intervention with benchmarking. The incidence of PPI prescription within the internal medicine department was compared to the surgical department, which served as the control. The study was 36 months in duration, examining a total of 44,973 admissions. Although patients within the internal medicine department had a higher rate of PPI prescription on admission than surgical department (44.9% versus 23.3%), the annual incidence of new PPI prescription was lower within the internal medicine (19, 19, 18 and 16%) in years 2014, 2015, 2016, and 2017 compared to surgical annual rate (30, 29, 36, 36%). The interventional group decreased new PPI prescriptions by 18.1% compared to the control group

32.8%. Del Giorno et al. (2018) suggested that clinical practice change resulted from active, continuous dissemination of evidence-based data with clinical expert feedback.

Clyne et al. (2015) performed a cluster-RCT utilizing a multi-strategy intervention to address potentially inappropriate prescribing (PIP) in the geriatric population. PPI prescription was the most commonly identified PIP. The researchers recruited 190 patients from 21 primary care practices. The multifaceted intervention included 1) pharmacy-led 30-minute medical provider educational session on PIP, 2) alternative pharmaceutical treatment algorithms and 3) tailored patient medication summary handout. Clyne et al. (2015) showed the intervention group had lower odds of having PIP [adjusted Odds Ratio [aOR] =0.32; 95% CI, 0.15-0.70; p = .02] and a significantly lower mean number of PIP drugs, 0.70 versus 1.18 from the control group. The multifaceted intervention was effective in decreasing PPI prescription [aOR =0.20; 95%, CI, 0.14-0.68; p = 0.04].

Walker et al. (2019) initiated a gastroenterology (GI) fellow-led PPI stewardship program. In their quality improvement pre-post intervention study, the authors created a PPI treatment flowsheet, incorporating guidelines derived from multiple GI societies. The PPI algorithm guided the identification of inappropriate PPI prescription and subsequent tapering of the medication. The authors used a multifaceted strategy: 1) educational session, 2) guideline-based PPI algorithm, and 3) stepwise documentation template incorporated into the medical record. If the clinical indication for PPI use was not ascertained using EMR or patient interview, the authors provided a written feedback to the patient's primary care provider to further assess the appropriateness of continued PPI use. Walker et al. (2019) showed a 23% reduction in the incidence of inappropriate PPI use after implementing the intervention.

Synthesis of Literature Review

The review of literature demonstrated potentially 66% of patients were inappropriately prescribed a PPI based on dose, duration, or indication (Scarpignato et al., 2019). One third of the PPI prescriptions in 69,352 patients examined by Mafi et al. (2019) were potentially low value because they lacked long-term guideline-based indications. PPIs were associated with a myriad of adverse side effects including nephrotoxicity, osteoporosis, hypomagnesemia, increased risk of infection secondary to *Clostridium Difficile* and COVID-19, and multiple drug-drug interactions (Almario et al, 2020; De Roza et al., 2018; Mafi et al., 2019; Ren et al., 2019; Tandum et al., 2019). In adults with cirrhosis, PPIs were associated with increased morbidity and mortality (Bajaj et al., 2018; De Roza et al., 2019; Tantai et al., 2019).

There continues to be a gap in PPI prescription compliance in the institution of study, despite an indication verification incorporated within the EMR as described in Appendix A. The literature suggested that PPI prescriptions were continued long after the initial appropriate indication (De Roza et al., 2019). The goal was to improve patient outcomes by promoting discontinuation of PPI when appropriate for the purpose of preventing potential iatrogenic complications, including HE, SBP, hospital readmissions and mortality (Bajaj et al., 2018; Dam et al., 2016; De Roza et al., 2019; Hung et al., 2018; Tantai et al., 2019).

According to Tomasone et al. (2020), education combined with an organization level intervention, such as an implementation team, was an effective strategy for medical provider practice change. The hepatology APP was in a pivotal position to lead a PPI stewardship program to improve the coordination of care for this patient population. The hepatology APP led the educational intervention, promoted the use of an evidence-based deprescribing guideline, and provided medical provider feedback regarding guideline compliance.

Gaps in Literature

The literature described a myriad of adverse side effects associated with PPI use; however, the data was based on observational or retrospective studies, which cannot establish a strong case for causality (Ren et al., 2019; Tandum et al., 2019; Willis & Duff, 2020). In addition, the literature supported minimizing the use of PPIs to guideline-based indications (De Roza et al., 2019; Hung et al., 2018; Tantai et al., 2019). However, practice guidelines for PPI use were vague regarding the indication, dose and duration of therapy for certain clinical scenarios (Willis & Duff, 2020). There was a lack of consensus on the best approach to discontinue PPI, whether dose reduction, abrupt discontinuation, or transition to as needed use was the appropriate approach (Willis & Duff, 2020). Implications for future research include a prospective RCT examining the efficacy of evidence-based deprescribing guidelines in various settings: hospital, long term care facilities, and outpatient clinic.

CHAPTER FOUR: METHODS

Project Design

There were two components to the QI project: patient data collection and education aimed at clinicians. The primary outcome variable was the incidence of inappropriate PPI prescription and the secondary outcome variable was the change in clinician knowledge level. The first component of the QI project was a quasi-experimental design comparing non-equivalent groups using a convenience sample. The proportion of low-value PPI was measured over one month duration before and one month duration after the implementation of the PPI Clinician Update and hepatology APP stewardship. The second component of the DNP project was an educational intervention entitled “PPI Clinician Update.” Knowledge level of providers was measured using a one group pre-posttest design with a total of ten questions.

The DNP QI project was in compliance with the Collaborative Institutional Training Initiative (CITI). The Institutional Review Board (IRB) for both the University of California, Los Angeles (UCLA) and institution of study were consulted and confirmed that a full IRB authorization was unnecessary as the QI project design used de-identified EMR data for patient information. The educational intervention was applied to staff as opposed to patients and was voluntary.

Setting, Sample, Sample Size Calculation, and Statistical Analysis

The QI project was performed in a single inpatient transplant medical center in Los Angeles. The educational intervention identified and recruited a convenience sample, who most frequently consulted with the hepatology service. A total of 30 clinicians were eligible. There were seven hospitalists, seven GI fellows, four GI attendings, one GI NP, one hepatology NP, two liver transplant pharmacists, two liver transplant PA, two liver transplant surgical fellows, and four hepatopancreaticobiliary NP. A G*power analysis indicated a sample size of 27 participants allowed detection of a moderate effect size (0.57) using a paired t-test with a one-tailed p-value of 0.05 and a power of 0.80 (Heinrich Heine University [HHU], 2021).

A convenience patient sample was used to measure the incidence of low-value PPI prescription before and after the implementation of an educational intervention. Inclusion criteria were as follows: hospitalized patients followed by hepatology service, 18 years old or older, diagnosed with cirrhosis, and a PPI prescription. A patient sample of 54 before and after the intervention would allow detection of medium effects with power .80 and one-tailed alpha=.05 (HHU, 2021). For example, that would allow detection of a decrease in low value PPI from 50% to 25%. A smaller available sample of, for example, 26 at each time point would allow detection

of large effects, e.g. a decrease from 50% to 15%. The actual obtained sample size fell between these two sample sizes.

A paired t test was used to analyze the change in provider knowledge level. Chi square was used to examine the difference between pre-education proportion of low-value PPI prescription compared to post-education whereas the odds ratio was used to examine change in the incidence of PPI (Lind et al., 2015).

Procedure and Measures

Medical providers received a 20-minute live educational intervention entitled "PPI Clinician Update" using the zoom platform in order to respect social distancing guidelines to prevent the spread of COVID-19 infection. All participants received a two-page PPI handout, which included a PPI deprescribing evidence-based algorithm, that was content verified by a hepatology expert who was a faculty at the same institution (see Appendix D). The educational session agenda included the incidence of low-value PPI prescription in the general and cirrhosis population, proposed pathophysiology of gut dysbiosis, and adverse side effects of a PPI within the general population and cirrhosis. A significant portion of the educational session focused on the use of a guideline-based deprescribing algorithm in order to address the gap in literature regarding the lack of guidance for PPI discontinuation. A pretest with a survey was administered using a google document before the education and a posttest with a survey was administered using a google document one month after the education (see Appendix E and Appendix F). The 10-item pre and posttests were identical and developed by the study investigator followed by content verification by a hepatology expert at the same institution. There was no time limit for the pre-posttest. At pretest, pertinent provider demographic data obtained included: provider

licensure, practice specialty, gender, and years of practice. The pretest survey included barriers to verifying PPI indication (see Appendix F).

After the educational intervention, the hepatology stewardship begun. The medication review was incorporated into the hepatology APP workflow as a standard service provided by hepatology. The hepatology APP discontinued low-value PPI prescription at the time of discharge or within three days of admission, whichever came first. The medical providers involved with the care of the patient received a verbal and written constructive feedback.

In order to determine the incidence of inappropriate PPI, the study investigator performed a retrospective EMR chart review for all patients seen by hepatology with the diagnosis of cirrhosis and a PPI prescription for one month duration in December 2020 to serve as the baseline PPI incidence. One month after the education intervention, an EMR chart review was performed for one month duration in February 2020, which included hepatology stewardship and active medical provider constructive feedback. The patient information was entered by the designated hepatology APP into a deidentified excel spreadsheet. Pertinent demographic data obtained included: age, gender, ethnicity, etiology of liver disease, MELD score, and existence of co-morbid conditions. A PPI prescription was classified as inappropriate if the prescription did not meet the published gastroenterology society guideline approved indications for PPIs and the deprescribing algorithm developed by the Bruyère Research Institute that was incorporated into the PPI Clinician Update handout (Willis & Duff, 2020). A hepatology physician expert randomly examined the data set to evaluate the accuracy of the hepatology APP assessment and serve as consultant in controversial uses of PPI. A timeline for the DNP QI project was represented by a Gantt chart in Appendix G.

CHAPTER FIVE: RESULTS

The primary outcome variable of interest was the incidence of inappropriate PPI prescription, and the secondary outcome of interest was the change in the medical provider's knowledge level regarding PPI use. The following summarizes the results of the QI project.

Participant Demographics

A total of 30 medical providers were approached to participate in the QI project; however, only 26 completed the educational session and pre-posttest. The details of the participant demographics are summarized in Table 1. The project participants were predominantly medical doctors (69%), followed by APP (27%) and a pharmacist (4%). The majority were female (62%) specializing as a hospitalist (27%) or gastroenterology (35%) with one to two years of experience (34.6%).

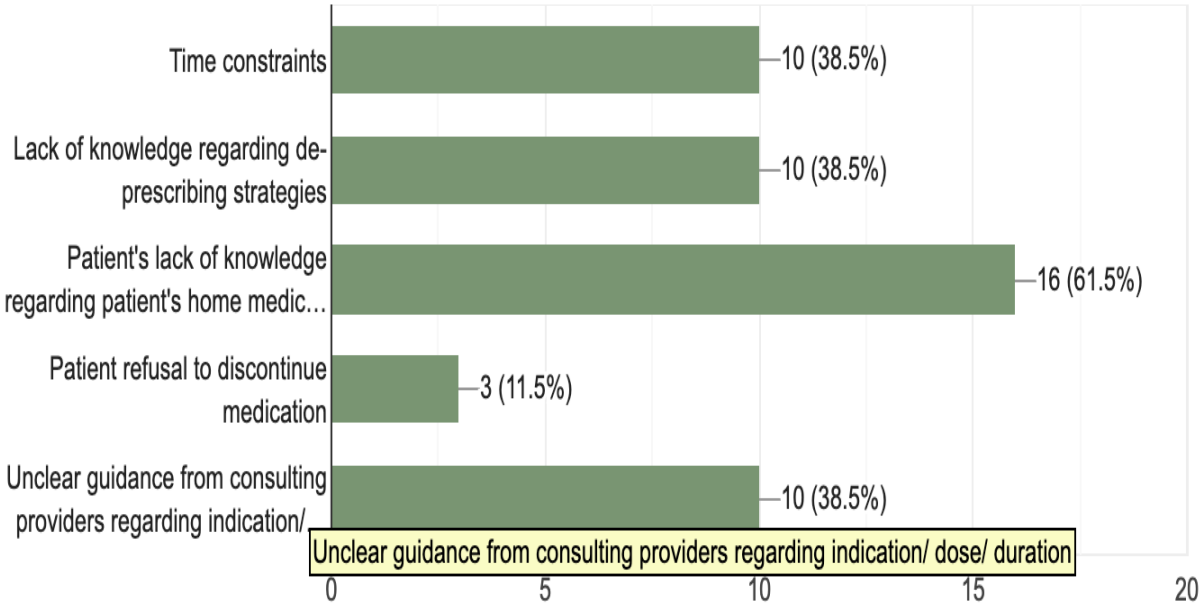
Table 1: *Medical Provider Demographic Data*

Characteristics	Frequency (n)	**%**
Professional Licensure	N = 26	
Medical Doctor (MD)	18	69%
Pharmacist (PharmD)	1	4.0%
Advanced Practice Provider (APP)		
Physician Assistant (PA)	4	15%
Nurse Practitioner	3	12%
Gender		
Male	10	38%
Female	16	62%
Specialty		
Hospitalist	7	27%
Hepatology	1	4%
Gastroenterology	9	35%
Liver Transplant Surgery	5	19%
Hepaticopancreaticobiliary Surgery	4	15%
Years in Practice		
Less than 1 year	5	20%
1-2 years	9	35%
3-5 years	4	15%
5-10 years	4	15%
Greater than 10 years	4	15%

Medical Provider Survey and Change in Knowledge

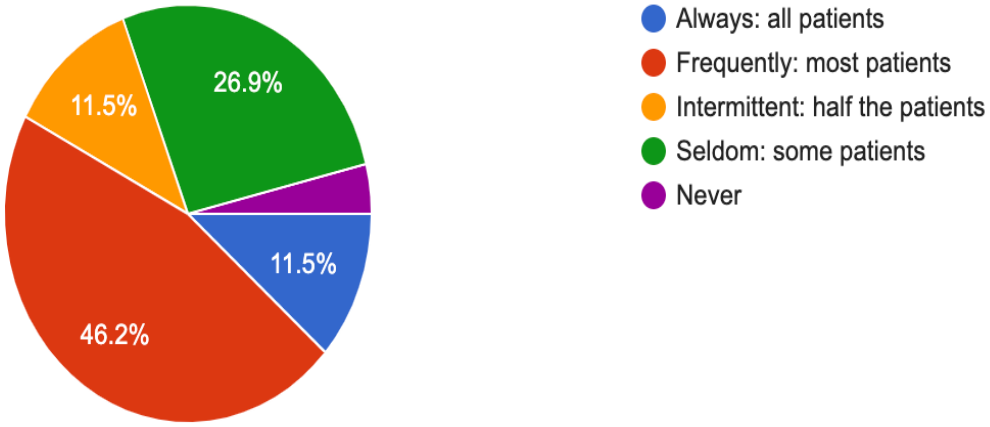
A survey was included in the pretest to further assess the nature of the clinical problem. Participants were asked to identify barriers to verifying PPI prescription indication. The majority of medical providers identified patient lack of knowledge regarding indication (61.5%) as the main barrier followed by time constraints (36.5%), lack of knowledge regarding deprescribing strategies (36.5%), unclear guidance from consulting providers (36.5%), and to a lesser extent patient's refusal to discontinue the medication (11.5%) (see Figure 1).

Figure 1: *Barriers to Verifying Proton Pump Inhibitor Indication*



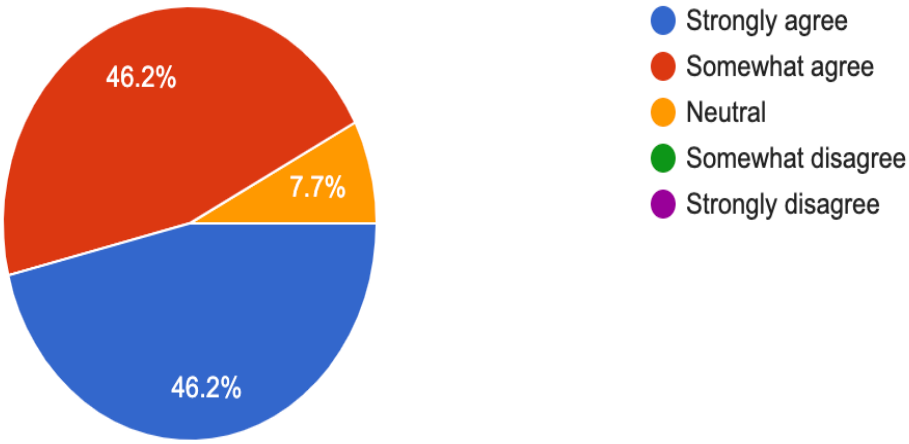
Study participants reported frequently (46.2%) continuing inpatient PPI prescription at discharge (see Figure 2).

Figure 2: *How often do you continue a proton pump inhibitor prescription initiated in the hospital to the outpatient setting?*



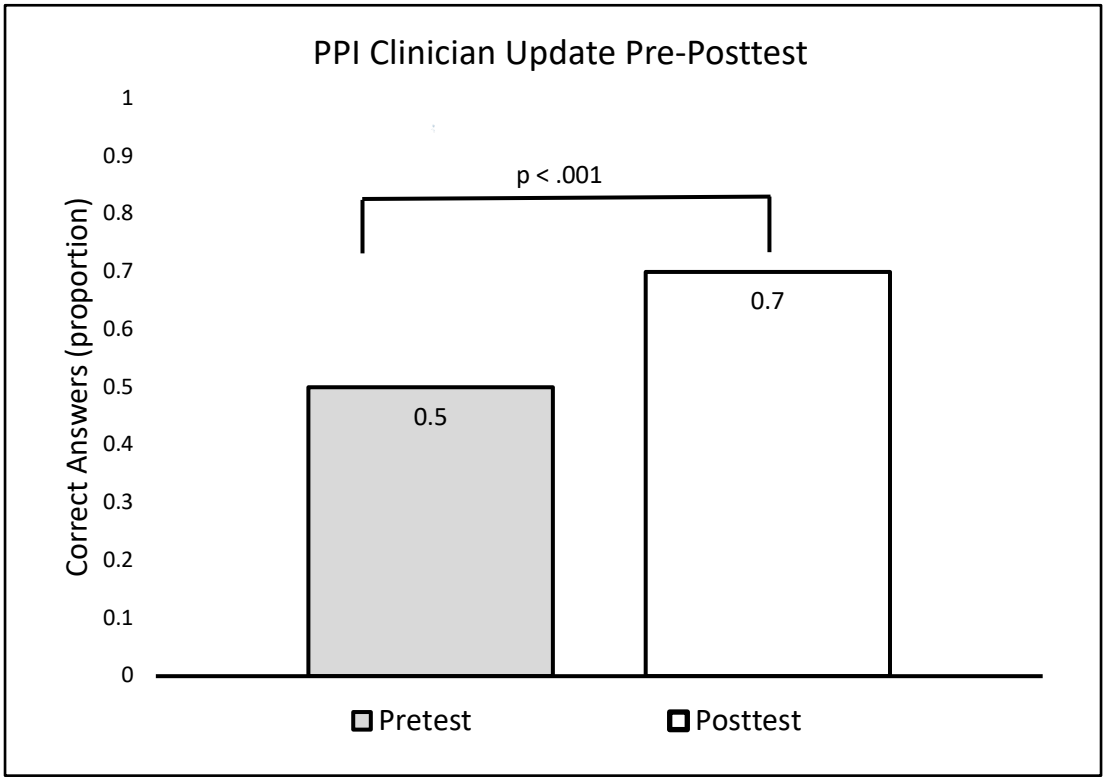
One month after the educational intervention, medical providers were asked to complete a knowledge posttest and report whether their prescribing behavior had changed as a result of the intervention. The posttest survey indicated a positive response to the educational intervention, wherein 46.2% of study participants strongly agreed that there was change in their medical practice in response to the information received (see Figure 3).

Figure 3: *Reported Change in Clinician Behavior After Education Session*



The pre-posttest was analyzed using a paired t-test, which revealed a statistically significant increase in mean proportion of correct answers in the test scores ($p < .0001$) (see Figure 4).

Figure 4: *PPI Clinician Knowledge Pre-Posttest*

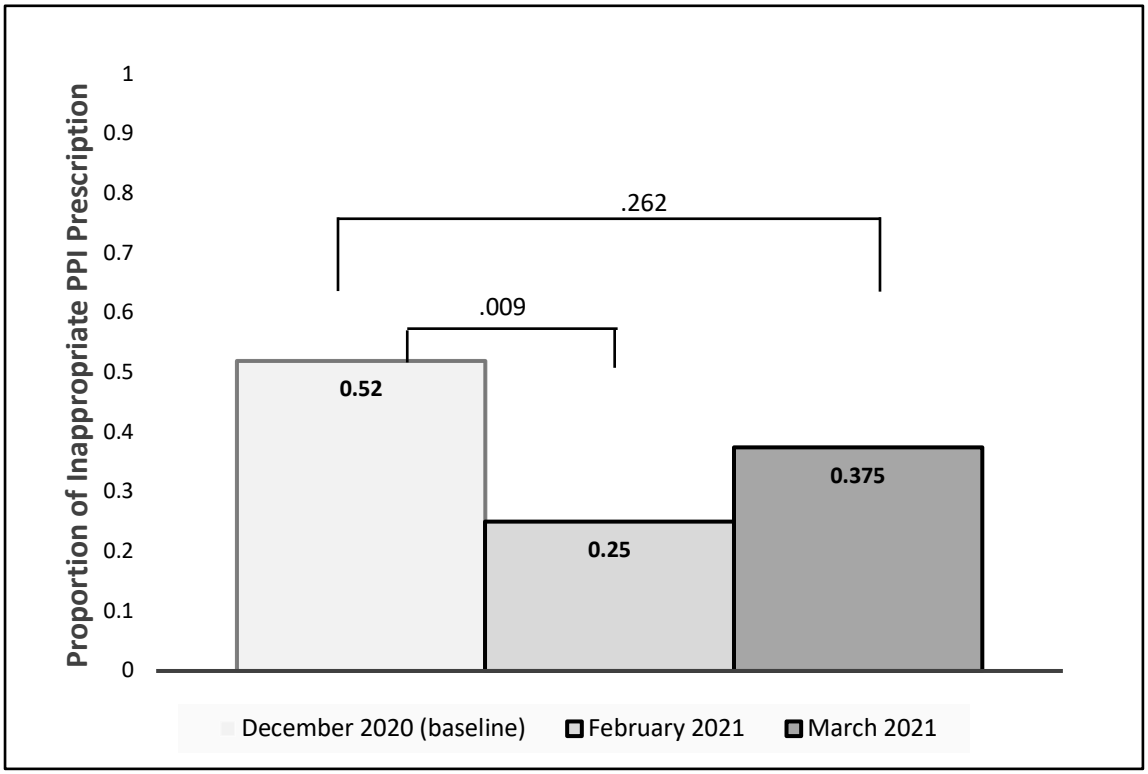


Incidence of Inappropriate PPI

The non-equivalent patient groups assessed for inappropriate PPI were compared using a chi square test. The patients evaluated pre- and post-intervention were typical of hospital clients. The pre-intervention group had an average age of 60 years old, 28% male, 50% Hispanic, 95% of whom had decompensated cirrhosis, 43% with alcohol induced liver disease as the underlying liver etiology associated with an average MELD score 23, MELD sodium 25. The post-intervention group had an average age of 59 years old, 61% male, 57% non-Hispanic, 93% of whom had decompensated cirrhosis, 36% with alcohol induced liver disease as the underlying liver etiology associated with an average MELD score 24, MELD sodium 26. There was a

statistically significant decrease from pre- to one-month post-intervention in the incidence of inappropriate PPI use from 52% (23/44) to 25% (11/44) (p = 0.009) (see Figure 5). In order to determine the sustainability of the educational intervention without hepatology stewardship, the incidence of inappropriate PPI was measured for one month duration in March 2021 without active hepatology stewardship. Baseline PPI incidence in December 2020 was compared to March 2021, which revealed an overall lower percentage of inappropriate PPI prescription 52% (23/44) to 38% (12/32); however, it was not statistically significant p = .262. The most common PPI indication identified on the Epic EMR was continuation of an outpatient medication that was not supported by an Epic diagnosis or an appropriate documentation.

Figure 5: *Incidence of Inappropriate PPI prescription*



CHAPTER SIX: DISCUSSION

The educational intervention combined with hepatology stewardship resulted in a reduction of inappropriate PPI prescription from 52% (23/44) to 25% (11/44). The reduction in

inappropriate PPI prescription was likely the result of an increased awareness regarding PPI use. We found that an educational intervention was effective in increasing knowledge regarding appropriate PPI use. There was an increase in mean test scores from 0.5 to 0.7 ($p < .001$) between the pre and posttest, which were one month apart, indicating medical providers retained the information over time. We also found that hepatology stewardship was an important component to the intervention because the incidence of inappropriate PPI rose from 25% to 38% once the hepatology stewardship was discontinued. The data suggested that sustained change required continuous constructive feedback leading to sustained awareness regarding PPI use. Tomasone et al. (2020) showed similar findings wherein organizational level intervention such as an implementation team was more effective in changing clinician behavior compared to education alone. Del Giorno et al. (2018) showed similar positive results in their longitudinal RCT, which revealed that active, continuous dissemination of evidence-based data with clinical expert feedback performed over a three year period was effective in obtaining lower incidence of inappropriate PPI over the three years implemented.

The baseline incidence of inappropriate PPI prescription (52%) was similar to the incidence described in literature (40 to 60%) (Al-Aly et al., 2020, Helgadottir & Bjornsson, 2019; Ikeji et al., 2019; Mafi et al., 2019). The medical provider survey identified the patient's lack of knowledge regarding the indication for a PPI prescription as a main barrier to verifying PPI indication in the hospital. The medical record review revealed that continuing prior to admission medication was the most common indication for PPI use documented on Epic EMR. Clinicians likely continued home medications assuming the indication continued to be appropriate. However according to De Roza et al. (2019), PPI prescriptions were often continued long after the initial appropriate indication expired.

Limitations

The limitation of the one group, pretest posttest design was threat to internal validity secondary to testing, indicating that the change potentially occurred secondary to repeated testing particularly in a short period of time. The limitation of the hepatology APP-led stewardship was threat to internal validity as the design was a quasi-experimental with convenience sample, which may possess selection bias, because it lacked the element of control obtained from random assignment (Lind et al., 2015). Therefore, inferring causality was difficult. In addition, the data was obtained from the EMR, which can pose a threat to construct validity. EMR review assumed that the record was accurate and complete. A patient may fail to report a diagnosis of GERD, which in turn, was not added into the EMR. The patient can then be misclassified as having low-value PPI prescription wherein reality the prescription was valid. Furthermore, the incidence of low-value PPI prescription may be underestimated because the EMR may not provide the duration of PPI prescription. A patient with cirrhosis and a PPI prescription with a diagnosis of GERD may be mislabeled as an appropriate PPI prescription; however, the patient may have had the prescription for over a year without re-assessment making the prescription low-value. Furthermore, there was a threat to external validity because the QI project used a small, convenience sample focused on one department.

Implications for Practice and Sustainability Considerations

Ultimately, the DNP QI project was a pilot study. The project hoped to serve as the first step in addressing the gap between evidence-based data and medical provider practice. There was over-prescription of PPI within the institution of study. Contributing to the over-prescription of PPI was the lack of documentation regarding the indication and duration. Future considerations to improve clinical practice include an EMR documentation template as described

in the QI project performed by Walker et al. (2019). Clear documentation would allow medical providers to track the indication and duration of the medication without having to rely on patient's level of knowledge regarding medication indication. On admission, the hospitalist and the pharmacist would need to perform a thorough prior to admission medication review. If the indication of the PPI prescription is unknown, the clinician can implement the deprescribing algorithm. At discharge, the patient will be given instructions regarding follow up with outpatient providers included in their after visit summary (AVS). The discharge note can be electronically routed to outpatient providers if within the same Epic EMR or faxed.

In order to promote sustained practice change, the PPI stewardship was incorporated into the workflow of the hepatology APP. Stewardship appeared to be a key component of the intervention to achieve a statistically significant decrease in the incidence of inappropriate PPI. The institution of study was an academic institution, and APPs served as the continuity of care. Future considerations for institution-wide implementation to other departments include a hospital wide educational intervention incorporated within the health stream educational module followed by the mobilization of APPs to serve as PPI stewards.

Future research could examine the role of the EMR. The deprescribing PPI algorithm could be incorporated in the Epic EMR for medical provider guidance, targeting admitting medical providers and pharmacists who perform prior to admission medication review. Future investigation for sustainable institution-wide change could examine the role of a built-in EMR prescription hard-stop for PPIs without the appropriate corresponding ICD-10 diagnosis, which subsequently would lead to an EMR-prompted hepatology or pharmacy review prior to renewal of a PPI prescription after an eight week duration of therapy.

CONCLUSION

PPIs were frequently prescribed to patients with cirrhosis. Review of PPI indication revealed that the most common reason for inappropriate PPI prescription was due to a continuation of a home medication without verifying the indication. An educational intervention that incorporated a PPI deprescribing algorithm was effective in increasing knowledge amongst medical providers. Education combined with hepatology stewardship were effective in decreasing the inappropriate PPI prescriptions in the inpatient setting and serve as a promising first step in this quality improvement initiative. The data suggested that hepatology stewardship was a key intervention in sustaining medical provider behavioral change because the incidence of inappropriate PPI rose in the absence of PPI stewardship. The repetitive constructive feedback re-enforced the information discussed during the educational session and led to an increased awareness of PPI prescription appropriateness in subsequent patients.

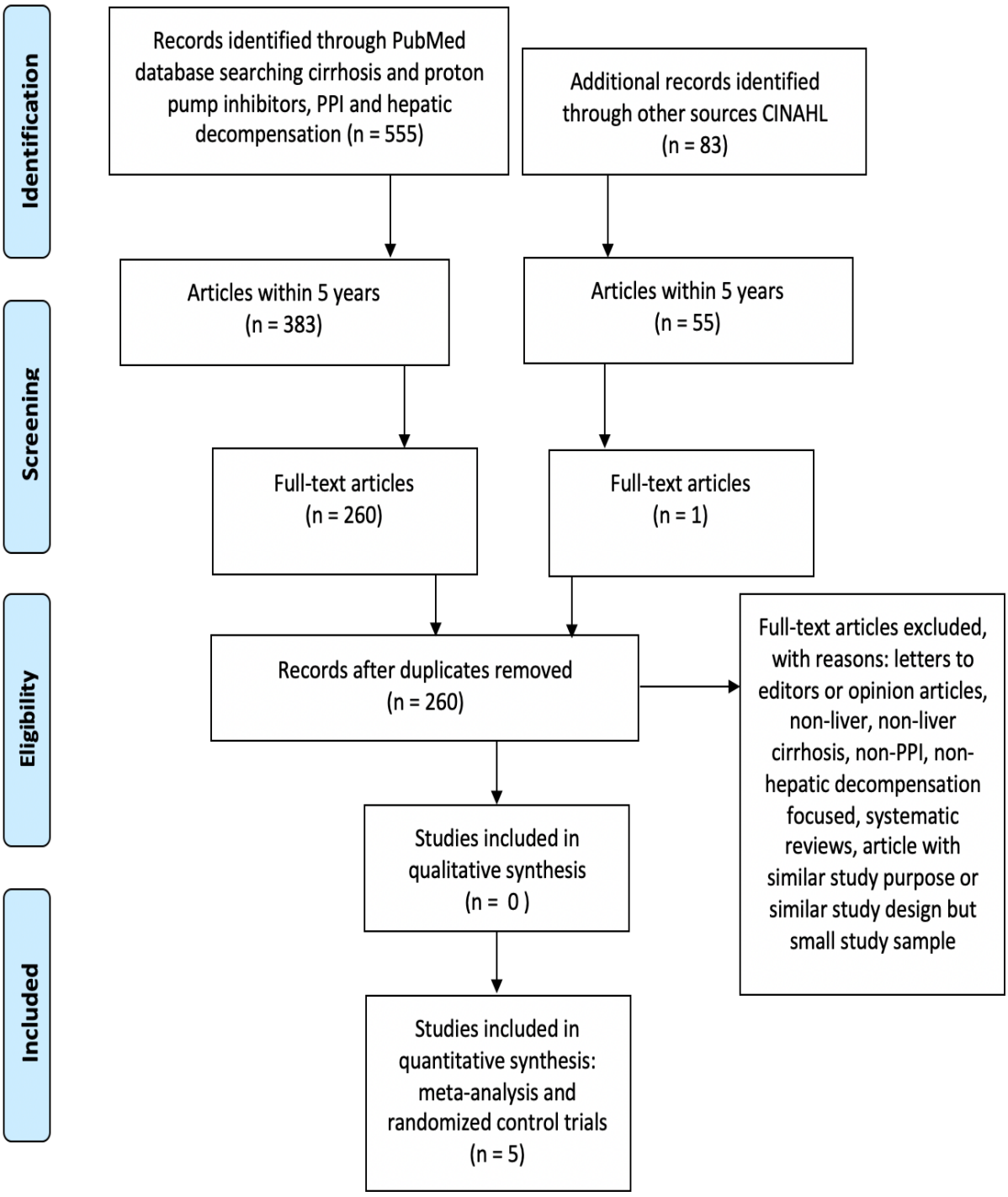
APPENDICES

Appendix A: Epic Institution-Approved Indication for Proton Pump Inhibitor Prescription

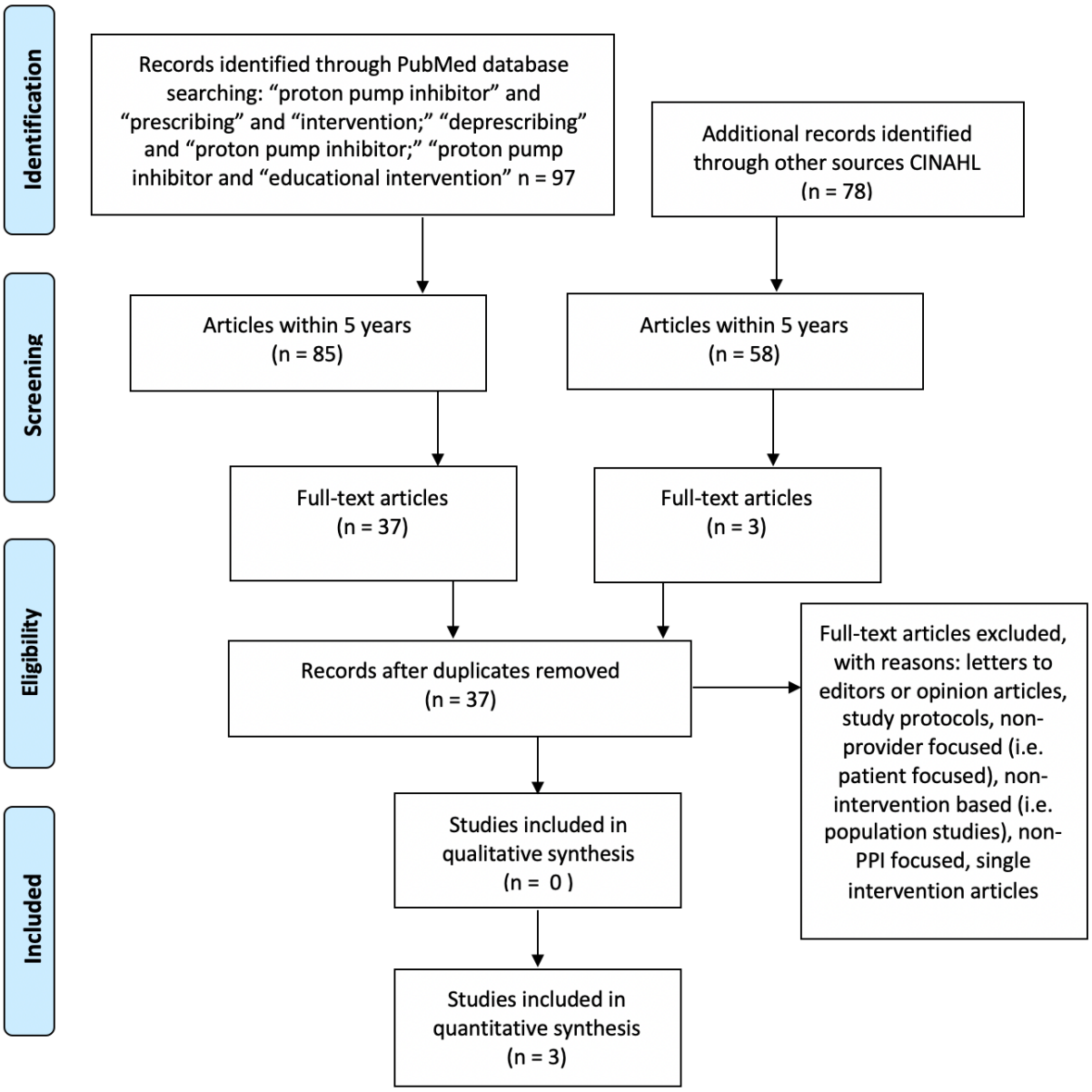
Pantoprazole may be used for stress ulcer prophylaxis if the patient meets one of the listed indications:

i. Treatment of gastrointestinal bleed, Gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD)
ii. Concurrent use of clopidogrel, anticoagulant or scheduled NSAID and aspirin
iii. Concurrent chronic steroids
iv. Gastritis
v. Esophagitis
vi. Transplant patient
vii. Platelet less than 100,000
viii. Jehovah's Witness
ix. Post-esophagectomy or post-op gastric bypass
x. High risk traumatic brain injury

Appendix B: Proton Pump Inhibitors and Cirrhosis Review of Literature



Appendix C: Deprescribing Proton Pump Inhibitors Interventions



Appendix D: FAQs Proton Pump Inhibitors in Liver Cirrhosis: An Update for Clinicians

FAQs for Clinicians

Proton Pump Inhibitors in Liver Cirrhosis

What's the problem?

Proton pump inhibitors are overly-prescribed. [1,13,16,19]

- ❑ Since introduced in 1989, PPI has become one of the most commonly used medication worldwide, accounting for $11 billion in expenditures annually[14]
- ❑ 15 million (7.8% of adult population) in the U.S. have a PPI prescription.[1]
- ❑ Between 40%- 60% are **inappropriate** PPI prescription based on dose, indication and long-term duration not tested nor approved by FDA [1,7,10, 13,16,19].
- ❑ 40-80% patients with cirrhosis are prescribed PPI[4]
- ❑ 2/3 of hospitalized patients with cirrhosis without clear indication[5]
- ❑ PPI dose-dependent increased risk for COVID-19 infection[2]

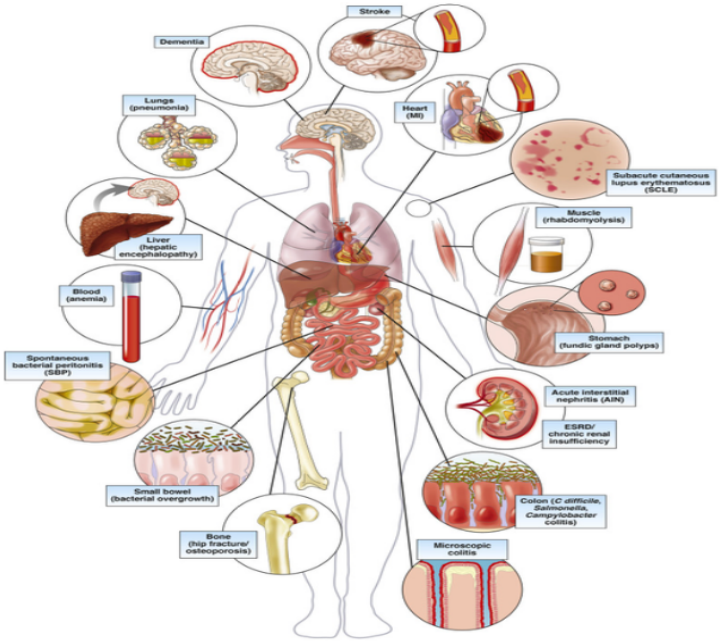
Pathophysiology

Gut dysbiosis: PPI disturbs gut microbiome balance leading to increased **gut barrier dysfunction subsequently increased bacterial translocation** and **hyperammonemia** [3,4,5,8,17,19]

Adverse Effects of PPI in Cirrhosis

- **Increased Mortality** [5, 8,9]
- **Re-admission rate** [3,5]
- **Spontaneous bacterial peritonitis** [3,4,5,16]
- **Hepatic encephalopathy** secondary to hyperammonemia from gut dysbiosis [4,5,9,16,17]
  - First episode of HE
  - Worse presentation of HE

Non-Liver PPI Adverse Effects [18]

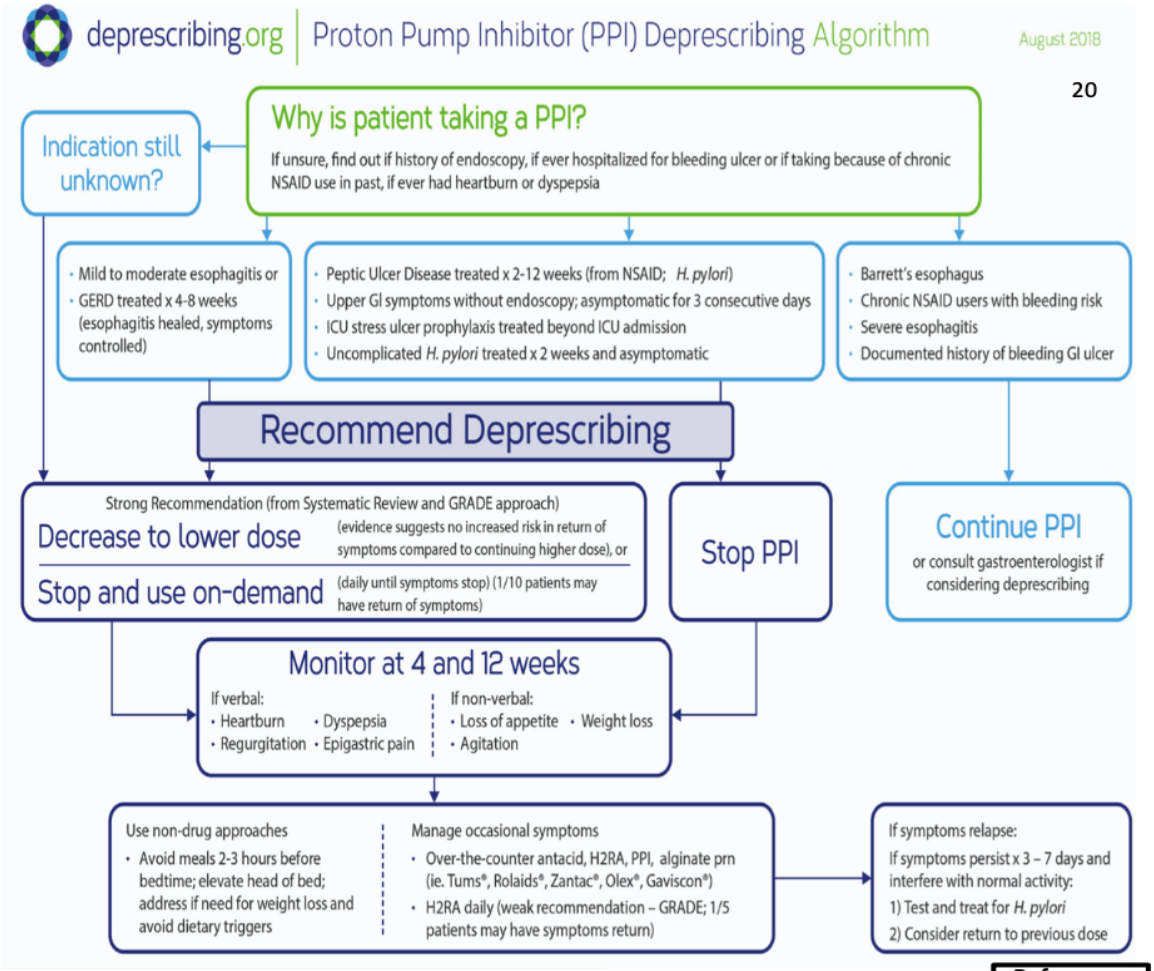


Juvelyn Palomique, MSN, RN, ACNP-BC

Side 1

PPI Use in Patients with Liver Cirrhosis

- ❑ **Short 10day course,** for **post banding ulcer prophylaxis** may have role to decrease size of ulcer, but lacks data to support decreased bleeding risk[11,16]
- ❑ **Stress Ulcer Prophylaxis**: critically-ill with high risk factor for GIB[15,18]
  - i. Mechanical ventilation > 48hrs
  - ii. Platelet < 50,000, INR > 1.5, PTT > 2x control
  - iii. H/o GI ulcer or GIB within 1 year
  - iv. NSAID or anti-platelet agents
  - v. Traumatic brain & spinal injury, burn injury
  - vi. ≥ 2 criteria: sepsis, ICU stay ≥ 1week, occult GI ≥ 6days, glucocorticoid therapy
- ❑ **No strong evidence** to support PPI use in management of gastric antral vascular ectasia (GAVE) or portal hypertensive gastropathy[6,12]



References

Side 2

Appendix E: Knowledge Pretest with Survey on Demographics and Reported Prescribing Behavior

Pre Test Demographics and Survey

I. Type of Medical Provider
   a. Physician
   b. Advanced Practice Provider: Physician Assistant or Nurse Practitioner
   c. Pharmacists

II. Practice Specialty
   a. Hospitalist
   b. Hepatology
   c. Gastroenterology
   d. Liver Transplant Surgery
   e. Hepatopancreaticobiliary Surgery

III. Years in Practice
   a. < 1 year
   b. 1-2 years
   c. 3-5 years
   d. 5-10 years
   e. > 10 years

IV. How often do you verify the proton pump inhibitor prescription indication?
   a. Always: all patients
   b. Frequently: most patients
   c. Intermittent: half the patients
   d. Seldom: some patients
   e. Never

V. Can you identify the barriers to verifying the indication for a proton pump inhibitor prescription?
   [ ] Time constraints
   [ ] Lack of knowledge regarding deprescribing strategies
   [ ] Patient's lack of knowledge regarding patient's home medication regimen and indication
   [ ] Patient refusal to discontinue mediation
   [ ] Unclear guidance from consulting providers regarding indication/ dose/ duration

VI. At the time of discharge, how often do you specify the end date of the proton pump inhibitor prescription or re-assessment date to the patient?
   a. Always: all patients
   b. Frequently: most patients
   c. Intermittent: half the patients
   d. Seldom: some patients
   e. Never

Knowledge Pre-Test

1. Since the introduction of proton pump inhibitors in 1989, it has become one of the most commonly utilized medication worldwide, accounting for $__ in expenditures annually.
    a. $1 million
    b. $50 million
    c. $80 million
    d. $5 billion
    e. $11 billion
2. According to literature, what percentage of PPI prescription is deemed inappropriate based on dose, indication, and long-term duration not tested nor approved by the FDA?
    a. 5-10%
    b. 10-15%
    c. 40-60%
    d. 70-80%
    e. 90-100%
3. Choose all that apply. Proton pump inhibitors are associated with the following complications
    [ ] Clostridium Difficile Infection
    [ ] Acute Interstitial Nephritis
    [ ] Increased all-cause mortality
    [ ] Osteoporosis
    [ ] Increased COVID 19 infection
4. Choose all that apply. Proton pump inhibitors are associated with the following complications in patients with liver cirrhosis
    [ ] Hepatic Encephalopathy
    [ ] Spontaneous Bacterial Peritonitis
    [ ] Increased Mortality
    [ ] Increased hospital re-admission
    [ ] Hepatocellular Carcinoma
5. Patients with Gastric Antral Vascular Ectasia (GAVE) or Portal Hypertensive Gastropathy (PHG) should be on a PPI therapy to decrease bleeding risk.
    a. No date to support use
    b. 7-10 days
    c. 14 days
    d. 30 days
    e. Indefinitely
6. Patients who had an endoscopic band ligation may be given a PPI for _____ to decrease ulcer size; however, there appears to be no strong data to suggest decreased risk of bleeding.
    a. No data to support use
    b. 10 days
    c. 30 days
    d. 60 days
    e. Indefinitely

7. In patients with a proton pump inhibitor prescription, it is safe to decrease dose or transition to as needed. Patients should have a follow up for return of symptoms in ____ weeks.
    a. Within 2 weeks
    b. 4 weeks to 12 weeks
    c. 6 to 12 weeks
    d. No follow up needed
8. What is the proposed pathophysiology leading to increased hepatic decompensation in the setting of proton pump inhibitor therapy
    a. Impaired drug absorption
    b. Disturbs gut microbiome balance leading to increased gut barrier dysfunction
    c. Increased bacterial translocation and hyperammonemia
    d. Both A & B correct
    e. Both B & C correct
9. Which of the following is correct regarding stress ulcer prophylaxis?
    a. Indicated for all patient discharged from the ICU
    b. Indicated for all patients admitted in the ICU
    c. Indicated for decompensated liver cirrhosis admitted in the ICU for fluid status optimization
    d. Indicated for critically ill patients in the ICU at high risk for GI bleeding
    e. Enteral H2 blockers preferred over enteral PPI blockers
10. Critically ill patients with the following criteria is considered high risk for clinically important gastrointestinal bleeding thereby justifying use of stress ulcer prophylaxis. Check all that applies.
    a. Mechanical ventilation for more than 48 hours
    b. Bleeding diathesis (platelet < 50,000), INR > 1.5, PTT > 2 times the control value
    c. GI ulcer or bleeding within the past year
    d. Concurrent non-steroidal anti-inflammatory or anti-platelet agents
    e. ≥ 2 of the following: sepsis, ICU stay > 1 week, occult GI bleeding ≥ 6 days, or steroid

Appendix F: Posttest Survey on Prescribing Behavior (Note that Knowledge Pretest [Appendix E] was also administered Post-test)

Posttest Survey

I. Did you change your PPI prescription practice based on the education you received
   a. Strongly agree
   b. Somewhat agree
   c. Neutral
   d. Somewhat disagree
   e. Strongly disagree

II. If you PPI prescription practice did not change, what were the barriers to changing practice?
   [ ] Time constraints
   [ ] Lack of knowledge regarding deprescribing strategies
   [ ] Patient's lack of knowledge regarding patient's home medication regimen and indication
   [ ] Patient refusal to discontinue mediation
   [ ] Unclear guidance from consulting providers regarding indication/ dose/ duration

Appendix G: Gantt Chart for DNP Quality Improvement Project Timeline

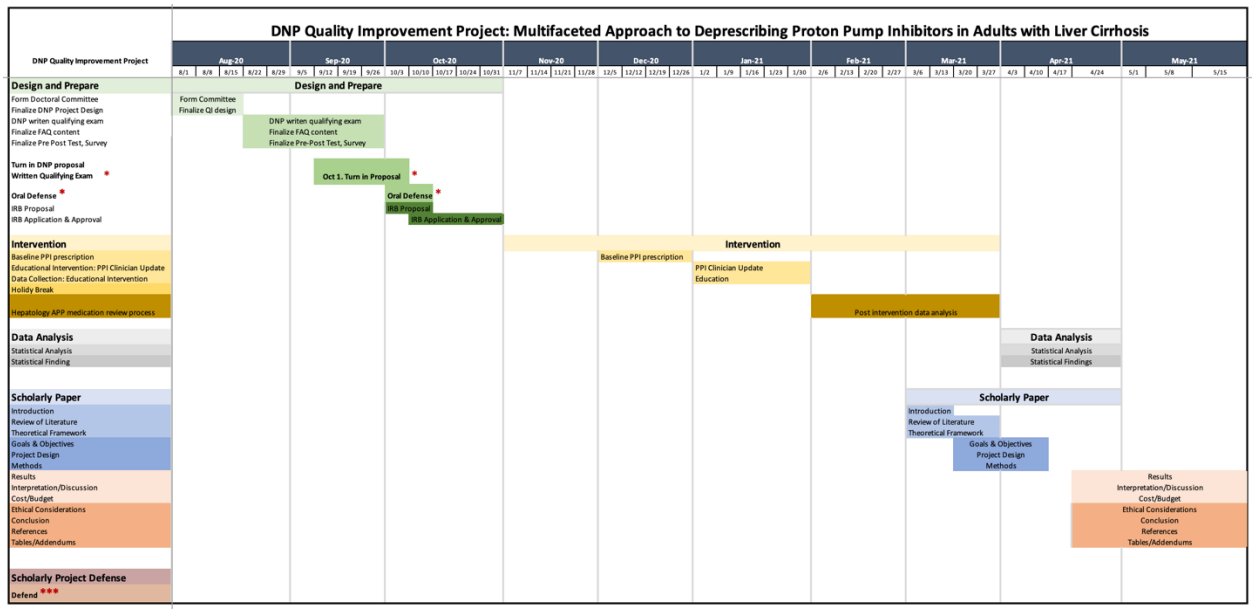


TABLE OF EVIDENCE

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS

Bajaj, J. S., Acharya, C., Fagan, A., White, M. B., Gavis, E., Heuman, D. M., Hylemon, P. B., Fuchs, M., Puri, P., Schubert, M. L., Sanyal, A. J., Sterling, R. K., Stravitz, T. R., Siddiqui, M. S., Luketic, V., Lee, H., Sikaroodi, M., & Gillevet, P. M (2018). Proton pump inhibitor initiation and withdrawal affects gut microbiota and readmission risk in cirrhosis. *American Journal of Gastroenterology, 113*, 1177-1186. https://doi.org/10.1038/s41395-018-0085-9	Determine effect of PPI use on gut microbiota and readmission in patients with cirrhosis.	Readmission study: Hospitalized patients with cirrhosis, followed at 30/90 post discharge. Exclusion: HIV, prior transplant. Microbiota study: Outpatient 137 patients with cirrhosis and chronic PPI (>1month) matched healthy controls (n=45) not on PPI. Longitudinal study: Exclusion: HE treatment, SBP prophylaxis, recent antibiotic/ probiotic therapy (<6weeks). Group 1: Cirrhotic studied before/after PPI initiation Cohort 2: Cirrhotic studied before/after PPI withdrawal (patients on chronic PPI) without indication	Readmission study: 343 inpatient (PPI on admission 151), 41 initiated on PPI on admission x14days. Binary logistic regression $p < 0.10$ on univariate analysis. Required n=161, alpha 0.05, power 80% Cross-sectional microbiota: multivariable regression models to analyze autochthonous taxa and oral taxa Longitudinal study: Cohort 1: Cirrhotic given omeprazole 40mg QD x 14days. Stool and blood collected at baseline and 14days. Cohort 2: pair t-test PPI withdrawn for 14days, patients not on PPI given	PPI use higher 30-day (p= 0.002), 90-day (p= 0.008) readmission independent of age, comorbidities, MELD, medications PPI uses regardless of cirrhosis: higher oral-origin microbiota. Cirrhotic on PPI: lower autochthonous taxa. PPI withdrawal in decompensated cirrhotic: significant reduction in oral-origin taxa compared to baseline.	Strength: close monitoring of study participants, defined PPI duration. Limitations: excluded hepatic encephalopathy patients. Only studied stool samples, not mucosal microbial taxa. Assumed all PPI had similar effects.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
			omeprazole x 14days then microbial analysis pre/post intervention		

De Roza, M. A., Kai, L., Kam, J. W., Chan, Y. H., Kwek, A., Ang, T. L., & Hsiang, J. C. (2019). Proton pump inhibitor use increases mortality and hepatic decompensation in liver cirrhosis. *World Journal of Gastroenterology, 25*(33), 4933-4944. doi: 10.3748/wjg.v25.i33.4933	Examine if PPI use increases mortality (defined as death or liver transplant) and rate of further hepatic decompensation (after index of admission at baseline). Examine impact of cumulative PPI dose exposure.	Data from Changi General Hospital database between January 2013- June 2017, using ICD10 coding. Cumulative daily dose (cDDD) ≥ 28 within hospitalization for HE. Hospitalized, decompensated cirrhosis, age > 18 N= 295 decompensated cirrhosis, 238 PPI users, 57 non-users. Elective admission excluded: TACE, RFA	Propensity score adjustment for 43 variables including baseline characteristics, co-morbidities, PPI indication, medication followed by Cox regression analysis. Further risk of HE by Poisson regression (95% CI, two tailed, $p < 0.05$. Landmark method: PPI user status definition: 3mo before to 6mo (-3 to +6) after index hepatic decompensation admission Additional landmark periods: -3mon to +3mo and -3mo to +9mo to validate primary outcome DDD: defined daily dose	PPI users had higher mortality compared to non-user [aHR= 2.10, (1.20-3.67); P=0.009.] seen in 6month and 9month landmark cohort [aHR3.44, 91.50-7.85); P=0.003] Longer PPI use (cDDD>90) associated with higher mortality compared to non-users [aHR=2.27, (1.10-5.14); P=0.038] PPI use had higher incidence of hospitalization for hepatic decompensation [aRR=1.61, (1.30-2.11); P<0.001] Dose dependent effect of PPI: cDDD>180 more likely to	Strengths: defined PPI duration, dose, survival analysis minimize selection, and indication bias Limitation: PPI use defined as physician prescription, no data on patient adherence. Adjust for antibiotic use but did not exclude rifaximin. Used all-cause mortality as objective measure. Analyzed decompensation severe enough to warrant hospitalization, did not analyze mild decompensation managed outpatient.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
				have admission for hepatic decompensation [aRR 1.91, (1.49-2.45); P < 0.001] compared to non-users	

Dam, G., Vilstrup, H., Watson, H., & Jepsen, P. (2016). Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. *Hepatology, 64*(4), 1265-1272. https://doi.org/10.1002/hep.28737	Examine association between PPIs and development of HE and SBP in patients with cirrhosis and ascites.	Used data from three, 1-year RTC studying satavaptan for ascites control, conducted July 2006- December 2008. Where? 3 target population, diuretic managed, diuretic plus paracentesis PRN, diuretic resistant managed via paracentesis primarily. N =1198 Patients followed every 4 weeks in clinic, all clinical events recorded	RCT Exclusion: prior/ present HE, TIPS, SBP or variceal bleed 10 days before randomization, HCC > Milan criteria, medication that potentiated cytochrome P450 3A pathway, increased QT interval Cumulative risk for HE computed using cumulative incidence function. Cox regression analysis to compare HE and SBP rates between PPI and non PPI users.	Original RCT study design results: Satavaptan did not affect HE, SBP, or have desired effect on ascites management. 865 cirrhotic patients with ascites, 39% (340) used PPI, 108 started during follow up, 52% used PPI at some point during follow up. 189 first time HE during follow up, cumulative 1 year risk 31% who used PPI at baseline vs 25% who did not [confounder-adjusted HR for HE for current PPI vs nonuse 1.36 (95%CI, 1.01-1.84)]	PPI is a risk factor for HE possibly 2/2 translocation of gut bacteria, which can lead to SBP. Strength: 3 large multicenter RCT. Limitation: PPI use varies over time. Study design was originally to examine satavaptan in ascites management.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
				No notable difference in HE precipitant factors between users and non-users, but PPI users had more severe HE. Overt HE [aHR=1.88; 95%CI, 1.21-1.91] Effect on HE risk did not depend on ascites severity 86 patients developed SBP [aHR for SBP with current PPI vs non-users 1.72 (95% CI, 1.10-2.69)].	

Hung, T. H., Lee, H. F., Tseng, C. W., Tsai, C. C., & Tsai, C. C. (2018). Effect of proton pump inhibitor in hospitalization on mortality of patients with hepatic encephalopathy and cirrhosis but no active gastrointestinal bleeding. *Clinic and Research in Hepatology and Gastroenterology, 48*, 353-359. https://doi.org/10.1016/j.clinre.2017.11.011	Examine if PPI associated with increased mortality in cirrhotic patients with hepatic encephalopathy (HE) and no GI active bleeding (GIB).	Using Taiwan Health National Health Database (covers 98% of Taiwan population) between January 1, 2010 -December 31, 2013, identified cirrhotic patients with HE without GI bleeding with and without PPI in the hospital setting. Exclusion: Variceal bleeding, Panendoscopy, IV PPI	1004 cirrhotic patients with HE and no active GIB who received PPI compared to control (using propensity score matching ratio at 1:4 ratio) 4016 cirrhotic patients with HE and no active GIB without PPI mortality rate at 30-day, 90- day and 1 year. Hazard Cox regression model analysis with adjustment for age, gender, and other comorbid disorders. CI 95%, significance level 0.05 Chi^2 test or Fisher exact test use to compare categorical variables. *t*-test used to compare	PPI increase short-term and long-term mortality in cirrhotic patients with HE and no active GIB. 30-day mortality 36.1%, 90- day 52.6%, 1 year 70.1% in PPI group compared to 27.5%, 41.7%, 62.4% in non PPI group. Hazard ratio (HR): 1.360 (95% CI: 1.208-1.532; P < 0.001), 1.563 (95% CI: 1.314-1.859; P < 0.001), and 1.187 (95%, CI, 1.008-1.398; P =0.040) for 30-day, 30-day to 90-day, and 90-day to 1 year mortality in patients taking PPIs.	Given large population, data with high reliability. PPI effect is likely class effect excluding rabeprazole, which either secondary to different pharmacokinetic pathway versus limited use. Limitations: First, data could not be associated with MELD vs Child-Pugh score because data set did not include the appropriate lab data, which was overcome by using Cox regression. Second, duration of PPI prior to admission unknown. Third, alcohol abstinence is important for improving survival; however, alcohol use habits unknown in the included patients. Third: unknown length of PPI treatment post discharge.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
			continuous variables.		

Del Giorno, R., Ceschi, A., Pironi, M., Zasa, A., Greco, A., & Gabutti, L. (2018). Multifaceted intervention to curb in-hospital over-prescription of proton pump inhibitors: A longitudinal multicenter quasi-experimental before-and-after study. *European Journal of Internal Medicine, 50,* 52-59. https://doi.org/10.1016/j.ejm.2017.11.002	Determine the efficacy of continuous monitoring and education regarding PPI over treatment, prescription inappropriateness and side effect profile in decreasing the incidence of new PPI prescription at time of discharge.	Inpatient Location: 5 public teaching hospitals in Switzerland, Italian speaking Control: all patients admitted in the surgical service Intervention: all patient admitted in the internal medicine service Source: EMR N= 44973 admission Duration: 36 months Intervention: Mean age 75, Female 49.9% Control: Mean age 67 Female 51.6%	Longitudinal, multi-center, quasi-experimental before-and-after study between July 1, 2014- June 30, 2017 Compare incidence of new PPI prescription at discharge between control (surgical department) vs internal medicine who receives "capillary" educational intervention and continuous transparent monitoring-benchmarking (face-to-face feedback, meetings, educational outreach) New PPI prescription measured quarterly and annually; chi square test used to	Rate of PPI prescription on admission: 44.9% (internal medicine) vs 23.3% (surgery) New PPI prescription 18.1% internal medicine vs 32.8% surgery. Decreasing annual rate of new PPI prescription in internal medicine department (19, 19, 18, 16%) compared to increasing rate of new PPI in surgical department (30, 29, 36, 36%) No significant increase in upper GIB admission/diagnosis Internal medicine: Odds of New PPI prescription	PPI prescription reduction over time (p for trend 0.02) internal medicine vs surgical (control) increased over time. Multifaceted approach facilitated provider attitude change, educational outreach with evidence based data more effective than passive guideline dissemination Strengths: multicenter, longitudinal, large population. Limitations: Potential difference in provider and patient characteristics, clinical impact of PPI prescription reduction not assessed.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
			trend changes overtime. Independent factors associated with new PPI prescription identified using multivariate regression analysis	increased with CM, indicating hospital acuity (OR 1.33, 95% CI 1.24-1.43, p , 0.001) decreased with age (OR = 0.99, 95%CI 0.99-1, p < 0.001), decreased odds of new PPI between 2014 vs 2017 (OR 0.82, 95%CI, 0.71-0.96, p = 0.014). Surgical department: Odds of new PPI increased with CM (OR 1.24, 95%CI, 1.19-1.30, p < 0.001), decreased in males OR 0.86, 95%cI, 0.80-0.92, p <0.001), increased over time OR 1.29, 95%CI 1.14-1.47, p < 0.001	

Clyne, B., Smith, S. M., Hughes, C. M., Boland, F., Bradley, M. C., Cooper, J. A., & Fahey, T. (2015). Effectiveness of a multifaceted intervention for potentially inappropriate prescribing in older patients in primary care: A cluster-randomized control trial (OPTI-SCRIPT study). *Annals of Family Medicine*, *13*(6), 545-553. https://doi.org/ 10.1370/ afm.1838	Test efficacy of a multifaceted approach to reduce PIP in older adults.	October 2012-September 2013 21 Primary care in Dublin, Ireland Location: urban 16, 5 mixed N=190 patients, Age: ≥ 70 years Mean age 77.1 (intervention), 76.4 (control) Male: 55 (intervention), 50 (control group)	Cluster-RCT Intervention group: Pharmacy led-discussion of PIP, web-based alternative treatment algorithms, patient information sheet. Control: standard visit, patient received standard medication information Compared to national data pharmacy database of dispensed medications Statistics: random-effects logistic regression, Bonferroni correction used to adjust for multiple comparisons Primary outcome measures:	Intervention group: mean PIP 0.70 vs control 1.18 (p = .02) Less likely to have PIP [aOR = 0.32; 95% CI, 0.15-0.70, P = .02] Reduction in PPI prescription [OR = 0.30; 95% CI, 0.14-0.68; P = .04] Lower incidence rate of PIP [ratio = 0.71, 95%CI, 0.50-1.02; P = .49) Less likely of PIP compared with national pharmacy database (crude OR = 0.4; 95% CI, 0.3-0.6) Most prevalent PIP drug: PPI. 53.3 (intervention),	Multifaceted approach more effected than single intervention Strong study design, high population retention Research pharmacist assessed outcome measures was blinded to GP allocation. Limitation: relatively low number of recruited GP practices limits generalizability Implication: reduction in PIP may indirectly improve health outcomes. Reduction in health care cost.

CITATION	PURPOSE	SAMPLE/SETTING	METHODS (Design, Interventions, Measures)	RESULTS	DISCUSSION, INTERPRETATION, LIMITATIONS
			1. proportion ofpatients with PIP drugs 2. mean number of PIP drugs per group (*t* test)	67.7 (control group)	

Walker, M. J., Crews, N. R., El-Halabi, M., & Fayad, N. F. (2019). Educational intervention improves proton pump inhibitor stewardship in outpatient gastroenterology clinics. *Gastroenterology Research, 12*(6), 305-311. https://doi.org/ 10.14740/ gr1238	Implement GI fellow-led PPI stewardship, assessing PPI prescription appropriateness using guideline-based PPI treatment flow chart.	Pre and post intervention: 8 weeks pre, 8 weeks intervention Outpatient VA and count GI continuity clinic Pre-intervention: 566 patients Intervention phase: 482 patients	Quality improvement: pre/post intervention. Baseline data = 8weeks historical data Intervention: PowerPoint educational session, stepwise documentation template, PPI treatment algorithm. Intervention data = 8 weeks	Pre-intervention: 46% (263 patient) PPI prescription. 49% (129) deemed inappropriate. GERD without dose titration (50%, 64 patients) BE BID dose (10%), indication unknown (14%). 8-week intervention: 224 (46%) PPI prescription. 130 (58%) appropriate PPI use. Appropriate PPI increased to 172 (77%) after intervention. Inappropriate PPI 23%	PPI continued post hospitalization without clear indication. Clinical notes deficient, leads to poor transition of care. Limitation: No PCP Feedback to ensure "unknown indication" addressed by PCP. GI fellows vested interest in decreasing PPI misuse. Strength: User friendly treatment algorithm, based on multiple GI society guidelines Future research: use Plan-Do-Act Cycle, assess intervention efficacy over longer time period (> 8 weeks), assess efficacy of algorithm in different departments

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