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Clinical Pharmacy services and medication utilization in Hospice Care

Aishwarya Kulkarni

CLINICIAL PHARMACY SERVICES AND MEDICATION UTILIZATION IN HOSPICE CARE

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By

Aishwarya Kulkarni

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Jordan R Covvey, PharmD, PhD, BCPS Associate Prof of Pharm Admin (Committee Chair)	Khalid M Kamal, MPharm, PhD Prof of Pharm Admin (Committee Member)
Mary Mihalyo, PharmD (former) Assistant Prof of Pharm Practice (Committee Member)	Vincent Giannetti, PhD (former) Prof of Pharm Admin (Committee Member)
Carl Anderson, PhD Interim Assistant Dean, Graduate School of Pharmaceutical Sciences	James Drennen, PhD Interim Dean, School of Pharmacy and Graduate School of Pharmaceutical Sciences

ABSTRACT

CLINICIAL PHARMACY SERVICES AND MEDICATION UTILIZATION IN HOSPICE CARE

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Thesis supervised by Dr Jordan Covvey

Background: As discussed within the guidelines from the American Society of Health-System Pharmacists (ASHP), pharmacists are an integral part of the hospice multidisciplinary team involved in optimizing the treatments. Methadone, a long-active opioid, is particularly useful in this population but may be clinically underutilized. Additionally, the cost share of medication utilization in hospice and palliative care is shifting towards hospice providers. The assessment of medication utilization and methadone use in this setting can help develop overall cost/clinical optimization strategies. Thus, there is a need to understand the use and expenditure of various medications and pharmacists' role in providing methadone use recommendations in hospice and palliative care settings that would facilitate the cost containment.

Objectives: The purpose of the study was to (1) identify the prevalence and acceptance of clinical pharmacists' methadone recommendation before and after admission to hospice/palliative care, and (2) identify the frequency, expenditure, and monthly mean cost of therapeutic medication classes belonging pain, pulmonary and anticoagulant medications categories.

Methods: The study was conducted in two phases. The phase I was conducted in two parts of data collection at DeltaCareRx hospice and palliative care site. A systematic literature review formed the basis of clinical pharmacist's role and significance in the multidisciplinary team of hospice and palliative care. The instruments for data collection were developed for the clinical pharmacists and student pharmacist researcher. Descriptive and inferential statistics of the collected data identified the prevalence of clinical pharmacist recommendations for methadone upon admission to hospice/palliative care and the acceptance of the pharmacists' recommendations for methadone after admission to hospice/palliative care. Phase II studied medication utilization at the hospice/palliative sites served by the pharmacy benefit manager (PBM) DeltaCareRx. Pharmacy claims data for six months of the year 2019 was obtained from DeltaCareRx. The data included information on the utilization of individual medications and their associated therapeutic classes, patient characteristics, and dispensing cost charged to the patients. Claims data were analyzed to identify the frequency in use, total expenditure, and the monthly average cost of each therapeutic class and the pattern in the utilization of therapeutic class based on the sex of the patients. The consumption of individual medications was calculated using defined daily doses (DDD), a methodology that analyses medication consumption and enables comparison across different months in a standardized manner.

Results: In total, the data collected on both instruments included 158 (99.3%) patients. The prevalence of pharmacist methadone recommendation was 37 (23.4%). The majority (26; 16.5%) of methadone recommendation were for switching to methadone as the maintenance treatment. Out of the 37 pharmacist recommendations, 5 (13.5%) were accepted by the physicians, and the physicians themselves implemented 3 (8.1%) recommendations. In phase II, the pharmacy claims data were obtained for six months (January, June, July, September, October, and November) of 2019. The data consisted of 487 unique therapeutic classes and 3,189 unique medications. Sympathomimetics, opioid agonists, and coumarin anticoagulants were the most frequently used therapeutic classes. The average cost per male/female patients was the highest ($64.82 and $67.70) for pulmonary medications. Medications such as albuterol, enoxaparin, and morphine had higher consumption levels.

Conclusion: The study provided valuable insights regarding clinical pharmacists' significant role in hospice and palliative care. A pharmacist's role in providing recommendations on

medication use to the patients can improve clinical/cost optimization in the setting. The data collection on pharmacists' recommendations on methadone demonstrates minimum medication use in the hospice and palliative care setting. There should be an increase in the use of this cost-effective medicine for pain management among the patients. The pharmacy claims data analysis implements that the rise in use of cost-effective medications from the individual therapeutic classes will help in higher cost savings at DeltaCareRx's client sites and reduce the provider's overall cost burden.

DEDICATION

I would like to dedicate this thesis to my newborn nephew and niece, Yunay and Mrunmayi . Thank you for bringing the joy in our lives.

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I would like to thank Dr. Jordan Covvey for her great inputs and constant support throughout my thesis work and time at Duquesne University. I highly appreciate the timely advice and direction that you provided. This work wouldn't have been possible without you. I would like to thank Dr. Kamal and Dr. Vince Gianneti for serving on my thesis committee and for being great professors throughout my journey at Duquesne. Thank you to all three for sharing your great knowledge and helping me solve problems either in professional or personal life.

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TABLE OF CONTENTS

Page

LIST OF TABLES

CHAPTER 1: BACKGROUND

I. Hospice and palliative care

a. Definition and prevalence

Hospice is compassionate care for patients who are in their terminal phase of life, defined as less than six months by the Medicare program.[1] It includes mainly pain and symptom management, and providing emotional and spiritual support as per the patient's needs. Palliative care is defined by World Health Organization (WHO) as "*a service which improves quality of life of patients through by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*".[2]

Hospice and palliative care services are paid for through both public and private insurance plans in the United States (US). For patients in the Medicare program, hospice is covered by Part A (Hospital Insurance) under the Medicare Hospice Benefit, established in 1982. Beneficiaries are eligible for the hospice benefit only if the hospice provider and their regular provider certify that the beneficiary is terminally ill (defined as a life expectancy of less than six months). Hospice care coverage for Medicaid patients depends on the life expectancy period established by the respective state in which they reside.[3] Palliative care is covered for beneficiaries under Medicare Part B (Medical Insurance). Medicaid patients can avail some palliative coverage as well, depending on the treatment they receive. Patients who are not eligible for hospice services due to a life expectancy of more than six months qualify for palliative care service.

Medicare defines four levels/types of hospice care, which varying needs of the patients. The first level of care is Routine Hospice Care (RHC) which is provided at the patient's residence, also known as routine nursing home care. The second level of care is Continuous Hospice Care (CHC), which is predominantly nursing care that focuses on maintaining pain control or addressing symptom crisis situations at the patient's home. The third level of care is Inpatient Respite Care (IRC), which provides a temporary support to the patient's primary caregiver. It can be offered in various settings, such as the hospital, hospice facility, or a long-term care facility that has enough 24-hour nursing personnel present. The fourth level of care is General Inpatient Care (GIP) which is offered for pain control or other acute symptom management that cannot feasibly be supplied in any other setting. GIP is offered when an additional care is required for managing symptoms of the patients. Among all levels of care, RHC service is the most

utilized type. In 2017, among all the hospice care in US, 98.2% of days of care were provided at RHC level, compared to CHC (0.2%), IRC (0.3%) and GIC (1.3%).[4,5]

In 2017, National Hospice and Palliative Care Organization (NHPCO) reported that 1.49 million Medicare beneficiaries received hospice care services, an increase of 4.5% from 2016.[4,5] The proportion of enrollees under Medicare Advantage plans who utilized hospice benefits have drastically increased from 26.8% in 2012 to 34.7% in 2017. This has resulted in a $18.99 billion payment by Medicare to hospice care providers in 2017, a 6.3% increase compared to $17.86 billion paid in 2016. The maximum spending based on level of care was on RHC service at 89.31%, and lowest on CHC at 1.77% of total spending.[5]

In case of palliative care services, fast growth has been observed as well. One of the reasons for this is the ability of palliative care services to improve quality of life (QoL) for both patients and their families. In 2019, 72% of hospitals with 50 or more beds were identified to have a palliative team, compared to 67% in 2015.[6,7] A report published by the Center to Advance Palliative Care (CAPC) assigned a letter grade (A to F) to almost all the states in the US as per the number of beds in the hospital and availability of a palliative care team in the same hospital. The letter grading rubric applied includes: "*A grade is assigned to a state in which over 80% of hospitals had palliative care programs, B grade to states with 61%–80% of hospitals with palliative care programs, C grade to states with 41%–60% of hospitals having palliative care programs, D grades to states with 21%–40% of hospitals having palliative care programs, and F grades to states with 20% or fewer hospitals having palliative care programs*".[7] As per the grading, three quarters of states in the US have either A or B grade, with more than 60% of hospitals with a palliative care team. The percentage of annual hospital admissions for palliative care increased slightly from 5.0% in 2016 to 5.3% in 2017.[7] The availability of palliative care depends on geography of the hospital and hospital size in terms of number of beds and tax status. Tax status is the predictor of access to palliative care. In 2019, as per the proportion of hospitals with palliative care based on tax status. Nonprofit hospitals regardless of hospital size (i.e. hospital beds facility 50-150, 151-300 and 301-350) were found to have higher proportion of palliative care services available. Access to palliative care was lowest for the for profit hospitals.[8]

b. Clinical importance

Hospice and palliative care focus on relieving pain and other symptoms in patients. The services offered in hospice setting focus on improving patient's remaining time left by providing comfort. Care additionally aids patients' families and caregivers during the time of illness by providing a support system.

One of the main aspects the care revolves around is providing quality of life to all the patients. All of the patient's needs are addressed during the time of illness, including physical, social, physiological and spiritual. [2]

Hospice improves end-of-life outcomes. The link between hospice care services and outcomes was identified through a research study, "*Quality of life matters: end of life care news and clinical findings for physicians,*" with data acquired from the Dartmouth Atlas of Healthcare Report (2012) and the American Hospital Association Survey (2012). It found that hospice care service was associated with high values of end-of-life care outcomes such as less hospital deaths (p=0.01), hospital stays (p=0.01), better pain control (p=0.01) and good patient ratings (P=0.01).[9]

Unlike hospice care, palliative care does not depend on prognosis of terminal illness. It mainly focuses on symptom management and psychological support. It achieves the desired clinical outcomes by comprehensive assessment and treating patient's physical, psychological, and spiritual symptoms. Palliative care plays a role in decreasing symptom burden, increasing communication between multidisciplinary teams and improving patient's treatment regimen. Initiating early palliative care in cancer patients has shown improvement in quality of life,[10,11] symptoms[11,12] and survival rates. [12,13]

c. Costs within the healthcare system

In 2017, 1.5 billion Medicare beneficiaries received hospice services, with a dramatic increase in resources utilized from $2.9 billion in 2000 to $17.9 billion in 2017.[14] Hospice and palliative care costs are shared by multiple entities, including Medicare, Medicaid, managed care or private insurance and other (such as charity and self-pay). The cost breakdown for each of these entities is 85.4%, 5%, 6.9% and 2.7% of the total expenditure, respectively.[15]

Medicare patients receive hospice coverage through their Medicare advantage plan. Payments are made from Medicare to hospice providers in a form of daily rates. As soon as a patient is enrolled in the hospice setting, the providers receive a fixed amount payment from Medicare, based on the four levels of care. For 2019, RHC for days 1-60 has a base rate of $196 per day and days 61+ has a base rate of $145, while CHC is $42 per hour, IRC is $176 per day and GIC is $758 per day.[14] The payment rates are changed annually by the inpatient hospice market basket index. The rate for the most common level of hospice care, RHC, was reformed in 2016 by CMS.[16,17] Originally, RHC was paid at a single rate, but now Medicare pays two per diem rates for RHC that includes a higher rate for the first 60 days of a hospice episode and a lower rate for days 61+, at $196 and $154 per day, respectively, in 2019.[16] The change in

the payment rates were made because hospices provide maximum care during the beginning and end of the episode and less during the middle phase.

Medicare pays the hospice/palliative care provider as per diem rate for the assigned level of care provided. The payment is fixed is regardless of the service provided to the patients.[18] Additionally, the payments are designed to limit the costs. An overall cap on the aggregate payment is applied to the Medicare hospice reimbursements along with caps on inpatient cap to limit the number of inpatient days.[19]

Hospice care services has proven to be cost effective compared to the care acquired in a hospital during the patient's last 180 days of survival, with the per diem expenditure in the inpatient setting far exceeding that for palliative/hospice care.[20] A cost-effectiveness study was conducted to evaluate the cost savings due to palliative inpatient admissions. The results of this study showed it to be more cost effective than the standard/usual inpatient care service in the hospital.[21] A retrospective data analysis of Medicare claims data demonstrated that beneficiaries enrolled in hospice 53–105 days before death saved $2,561 compared to a matched, nonhospice control population ($22,083 vs $26,466 $p<0.01$).[22]

II. Medication use in hospice setting

Beneficiaries covered under Medicare Hospice Benefit receive treatment to address symptoms, maximize comfort and improve quality of life. Under Medicare Part A, beneficiaries have access to only those drugs that are used for pain relief and other terminal illness conditions (inclusive of biologics which have palliative roles). Hospices utilize formularies, wherein all commonly used drugs for palliation and terminal illness management are included.

a. Policy changes with Medicare billing

There are instances when beneficiaries require medications not on the hospice formulary and/or covered by Part A. In this case, previous Medicare guidelines allowed inappropriate payments for these medications required to treat hospice related symptoms under the Medicare Part D benefit. However, in 2013, policy was changed to prevent these inappropriate payments. The letter stated that drugs and biologics when used primarily for the relief of pain and symptom control related to the terminal condition will be covered under the Medicare Part A per-diem payment. The medication will be covered under Part D only when it is not related to the patient's terminal illness.[23]

III. General role of pharmacists

Pharmacists are highly educated with regards to medications. They conduct comprehensive medical history reviews and perform medication reconciliation. Special attention is given to pharmacotherapy history, symptom assessment, and identification of drug-related problems. Pharmacists also provide patient counseling where they can identify inadequate treatment response or treatment-related adverse events.[24] In 2010, CMS published a certification process manual for hospice providers, recommending that each hospice care facility have a clinical pharmacist. The functions carried out by this pharmacist may include educating and training patients regarding drug management and assisting patients in treatment selection. They can also conduct outcome assessment for ensuring the quality of the service provided. They play a significant role in managing adverse effects and proving recommendation wherever necessary.[25]

The 2000 American Society Health System Pharmacist guidelines detailed pharmacist responsibilities and their scope of practice in contributing to the hospice care.[26] The listed roles of pharmacist included: (1) symptom management, (2) counseling and education of staff and family members, (3) ensuring adherence to the drug, (4) addressing financial concerns of the patients and (5) disposal of medication after patient's death. Further, ASHP published an updated report exploring extended involvement of the pharmacist in hospice and palliative care (PHC)[27]. It describes PHC services in two parts, including essential and desirable services. Roles and responsibilities for essential services include: (1) direct patient care, (2) medical review and reconciliation, (3) education and medication counseling and (4) administrative roles. Desirable services include: (1) direct patient care, (2) education, (3) scholarship and (4) administrative roles.

IV. Pain management within hospice/palliative care

Pain is a multidimensional experience of emotional and physical dimensions. The concept of total pain for terminally ill patients is made up of four components, including: (1) physical noxious stimuli, (2) emotional discomfort, (3) interpersonal conflicts, and (4) nonacceptance of one's own dying.[28] The ultimate key of pain management in end-of-life care is pain assessment. They focus on not only treating physical pain but also the emotional and interpersonal pain of the patient. The objective of end of life care is assisting the patient with pain reduction interventions and improving their functioning abilities as much as possible. There are organizations such as National Hospice and Palliative Care Organization (NHPCO), American Academy of Hospice and Palliative Medicine (AAHMA) , Center to Advance palliative Care

(CAPC) and others which publish guidelines/reports which can be useful for delivering hospice and palliative care.[29,30]

a. Clinical guidelines and outcomes of interest

Pain is classified in an unstructured manner despite being a common ailment among patients. A task force on taxonomy initiated by International Association for Study of Pain (IASP) provides a detailed classification of chronic pain.[31] It classifies chronic pain in two types; chronic primary pain and secondary pain. Chronic primary pain is characterized by disability or emotional stress, a more "nonspecific" pain. International Classification of Diseases 11th revision, "defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive, hierarchical fashion".[32] Chronic secondary pain is more specific pain represented by ICD-11. Additionally, WHO guidelines on "*Palliative care: symptom management and end of life care*" explains pain management in detail.[33] It recommends conducting pain assessment, assigning treatment based on the assessment and later on managing the symptoms due the treatments assigned. In 2017, the National Coalition for Hospice and Palliative Care published the '*Clinical Practice Guidelines for Quality Palliative Care, 4th edition,*' aimed to improve palliative care access to patients with serious illness by guiding the healthcare organizations across to integrate principles in their routine assessment and delivery of quality care.[29]

b. Medications used in pain management

Pain management in an end-of-life care setting begins with determining the patient's pain type. Assessment can be in terms of location of pain (visceral, somatic, neuropathic or nociceptive) or intensity of pain.[34] Determination of the type of pain assists providers in assigning appropriate pharmacotherapy. WHO's Pain Ladder provides guidelines for achieving pain management in cancer patients as well as patient with chronic and acute nonmalignant pain. The first line agents are non-opioids drugs such as acetaminophen and/or NSAIDS, used to treat mild type of pain. For treating moderate pain, the guidelines include administering an opioid such as hydrocodone or oxycodone along with or without acetaminophen/NSAID.[35] Patients with severe pain are advised to use stronger opioid therapies, due to their analgesic effect.[36] Some of the common opioid used in hospice care include morphine, buprenorphine, fentanyl, etc. An essential medication list for palliative care includes ibuprofen and morphine as a treatment for pharmacological pain management.[37]

c. Utilization of methadone in hospice care

Traditionally, methadone, a synthetic opioid, has been used for treating opioid dependence, but it also has significant utility in the treatment of chronic pain, where it has clinical and cost benefits over other opioids

which are used for pain management.[34,38] Methadone is considered to have a high bioavailability, long duration of action and is available in multiple dosage forms (oral, rectal, parenteral). [39] It also provides an option for treatment in patients with morphine allergy. Furthermore, it acts as a *N-methyl-D-aspartate* (NMDA) receptor antagonist, which provides utility in the treatment of neuropathic pain and a reduced propensity to develop opioid tolerance.[40,41,42]

Methadone is a high-risk medication, which makes it important for its administration and use to be monitored closely by a pharmacist. The medication can cause several important adverse effects, including QTc interval prolongation, respiratory depression, and drug accumulation. The long half-life of the drug is the consequence of accumulation in the body relative to amount of drug eliminated from the body.[43] The American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD), in collaboration with the Heart Rhythm Society (HRS), consulted an interdisciplinary panel to develop a clinical practice guideline on safer prescribing of methadone for treatment of opioid addiction and chronic pain. The guidelines recommend careful assessment and selection of patient prior to administering methadone, inclusive of patient education/counseling and a baseline ECG assessment.[44,45]

d. Role of pharmacists specifically in pain management

Pharmacists are a great source of timely advice to patients. They are available without appointments and at convenient locations to discuss any patient's onset of pain episodes.[46] A pharmacist-managed pain clinic resulted in a decrease in waiting for appointments and elimination of unscheduled visits for narcotic prescription. Their involvement resulted in close monitoring of pharmacotherapy, adverse events, and medication dosages. Pharmacists helped in facilitating communication between pain clinic staff, pharmacy department and physicians.[47] A systematic review and meta-analysis analyzed pharmacist role in chronic pain management at community and hospital settings. The identified roles included conducting medication reviews, specialized prescription delivery service, face to face consultation and providing recommendations to the physicians. These resulted in reduced pain intensity, improvement of physical functioning and patient satisfaction.[48]

V. DeltaCareRx

DeltaCareRx is a locally based pharmacy services organization that works with hospice and palliative care providers across the US. Duquesne University has a collaboration with the organization through Dr Mary Mihalyo, a clinical pharmacist faculty member in the School of Pharmacy.

a. Description of the organization

DeltaCareRx is a pharmacist-founded, pharmacist-owned, and pharmacist-operated pharmacy benefit management (PBM) company that works exclusively with and for hospice and palliative care providers, primarily community-based, not-for-profit hospice and palliative care organizations. Pharmaceutical care is provided through their mail order pharmacy and a nationwide network of highly regarded local retail pharmacies. DeltaCareRx has a mission to transform and improve the hospice pharmacy industry through business transparency, innovation, consistent customer service and community pharmacy relationships. The transparency is maintained through the creation of pricing models and innovative technologies designed to support clinicians. Furthermore, the organization is known for delivering quality, compassionate, cost-effective pharmaceutical care for patients with a life-limiting diagnosis.[49]

b. Services provided to hospices

DeltaCareRx provides local PBMs services to hospices. It facilitates medication availability from local pharmacies and optimizes cost-effectiveness. Additionally, they provide a facility known as inpatient innovation™ which is a Delta Care pharmacy installed in an inpatient unit. Mail order delivery is provided to the patient's house which is useful in case of medical crisis. They provide patient monitoring through their branch of service known as ADAPT (remote patient monitoring and, pharmaceutical care at home). It is created for remote patient monitoring and proving pharmaceutical care at home. ADAPT delivers therapeutic expertise, prescription dispensing options and technological innovation to improve clinical outcomes and effective cost control mechanisms. Additionally, report generation is made easy through their innovative web-based technology Deltalytics. These reports assist in understanding trends in prescription, matching benchmarking values and quality initiatives. They provide their clients with newest technology, education support and cost containment strategies.

VI. Problem statement

Pharmacists play an important role in hospice and palliative care. Their involvement in pain management has demonstrated desired clinical and cost outcomes. Despite many advantages of pharmacist's involvement and recommendations by ASHP, many hospice and palliative care organizations remain reluctant to include pharmacist in their multidisciplinary team. The practical demonstration of importance of a pharmacist recommendation and their role will make the idea of adding a pharmacist to the team stronger. Therefore, it is necessary to assess their involvement in the daily routine of hospice and palliative care. Their involvement can be assessed through the recommendation they provide to the patients

suffering with pain. Methadone is an effective medication to treat chronic pain and generates cost savings. Still it is found to be underutilized in hospice and palliative care settings. Therefore, it is necessary to understand whether pharmacist recommend this drug for pain management. If the provided recommendations have not been accepted by the physicians without a reason, it would demonstrate a gap in knowledge transfer regarding the appropriate use of the medication. One of the opportunities to understand the trend in use of methadone at hospice and palliative care sites is through Deltalytics. It is a web- based report generator innovated by DeltaCareRx. The reports generated contains the utilization value of each medication for each one of the DeltaCareRx's clients. These values are then compared to the industry benchmarking. This activity decreases unnecessary utilization of medication and encourages cost saving. Analyzing the reports would assist in understanding the pattern in use of methadone and other medications post the Medicare policy changes in 2013. Additionally, it will encourage the use of cost-effective drugs at the client sites.

VII. Study objectives/aims

Therefore, to further understand the importance and impact of pharmacist services in hospice/palliative care, the specific aims of the studies are as follows:

- Identify the impact of clinical pharmacist recommendations for methadone upon admission to hospice/palliative care services
- Evaluate differences in medication utilization across different hospice settings served by DeltaCareRx

CHAPTER 2: LITERATURE REVIEW

I. Rationale

ASHP guidelines describe the expansion of the clinical pharmacist roles in hospice and palliative care service.[27] Clinical pharmacists play different roles in patient counseling, optimizing medication use, and recommending or terminating medications in the provision of care.[26,50] The inclusion of a pharmacist in the hospice/palliative care has potential to improve clinical outcomes and demonstrate cost savings.[51]

Pharmacists are involved in direct contact of care in pain management given their accessibility compared to other healthcare professionals. Clinical pharmacists can conduct clinical pain assessments before and after administration of the treatment. They also can play an important role while selecting and monitoring appropriate therapeutic regimens for patients. Valgus *et al*. evaluated the impact of a pharmacist-led, interdisciplinary team intervention on cancer patients in an ambulatory cancer clinic setting. The intervention was found to improve symptom scores and use of medications in these patients.[52] A pharmacist is also an integral part of educating/training other staff members and family members. A systematic review and meta-analysis conducted by Benneth *et al*. reported the positive impact of pharmacist-led educational interventions on chronic pain patients.[53] As per the ASHP guidelines, roles

and responsibilities of a pharmacist in a hospice and palliative care multidisciplinary team can assist in improving patient's quality of life.[27]

There are many studies that have provided information on roles of a pharmacist in hospice and palliative care settings. However, the specific impact of clinical pharmacists in pain management in these settings has not been fully evaluated. Accordingly, it is necessary to identify the impact of pharmacist-led interventions or pharmacist involvement on clinical/cost outcomes in the treatment of pain in hospice and palliative care.

II. Objective

The objective of the systematic review was to: (1) identify available information on the extent of clinical pharmacist involvement in the pain management of hospice and palliative care patients, and (2) explore relevant roles of a pharmacist in achieving clinical/cost outcomes while participating in pain management of end-of-life care patients.

III. Search strategy

The systemic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[54] The articles were retrieved/assessed on three databases: PubMed, Embase and Scopus. The first search was done on PubMed using keywords including 'pharmacist,' 'hospice care,' 'palliative care,' 'pain' and 'pain management.' The search strategy from PubMed was then modified to suit Embase and Scopus search strategies. The keywords utilized in all the three databases are included below.

a. PubMed

((("Pharmacists"[Mesh] OR Pharmacist*[tiab] OR Pharmacist*[ot] OR "Pharmacy Service, Hospital"[Mesh] OR "Pharmacy Service"[tiab] OR "Pharmacy Service"[ot] OR "Pharmacist service"[ot] OR "Pharmacist service"[tiab])
AND
("Pain"[Mesh] OR "Pain"[ot] OR "Pain"[tiab] OR "Pain Management"[Mesh] OR "Pain Management"[tiab] OR "Pain Management"[ot] OR "Hospice and palliative Care Nursing"[MeSH] OR "Analgesics"[Mesh] OR Analgesic*[tiab] OR Analgesic*[ot])
AND

("Hospice Care"[Mesh] OR "Respite Care"[Mesh] OR "Respite Care"[ot] OR "Respite Care"[tiab] OR "Home Care Services"[Mesh] OR "Home Care Services"[ot] OR "Home Care Services"[tiab] OR "Home Care Service"[ot] OR "Palliative Care"[Mesh] OR "Palliative"[tiab] OR "Palliative"[ot] OR "supportive care"[tiab] OR "supportive care"[ot] OR "home hospice"[ot] OR "home hospice"[tiab] OR "Hospices"[Mesh] OR Hospice*[ot] OR Hospice*[tiab] OR "Bereavement care"[ot] OR "Bereavement care"[tiab])))

b. Embase

('pharmacist'/exp OR 'pharmacist*' OR 'hospital pharmacy'/exp OR 'hospital pharmac*' OR 'pharmacist intervention'/exp)
AND
('analgesia'/exp OR 'analgesi*' OR 'pain management index'/exp OR 'pain'/exp OR 'pain*' OR 'palliative nursing'/exp OR 'palliative nursing')
AND
('hospice care'/exp OR 'hospice care' OR 'hospice'/exp OR 'hospice*' OR 'palliative therapy'/exp OR 'palliative therapy' OR 'terminal care'/exp OR 'terminal care' OR 'respite care'/exp OR 'respite care' OR 'home care'/exp OR 'home care' OR 'supportive care'/exp OR 'supportive care' OR 'bereavement care'/exp OR 'bereavement care')

c. Scopus

(INDEXTERMS(Pharmacist*) OR TITLE-ABS-KEY(Pharmacist*) OR INDEXTERMS("Pharmacy Service, Hospital") OR INDEXTERMS("hospital pharmacy") OR INDEXTERMS ("pharmacist interventions") OR TITLE-ABS-KEY("Pharmacy Service") OR TITLE-ABS-KEY("Pharmacist service"))
AND
(INDEXTERMS("Pain") OR TITLE-ABS-KEY("Pain") OR INDEXTERMS("Pain Management") OR TITLE-ABS-KEY("Pain Management") OR INDEXTERMS("Hospice and palliative Care Nursing") OR INDEXTERMS("Analgesics") OR TITLE-ABS-KEY(Analgesic*) OR INDEXTERMS(analgesia) OR INDEXTERMS("pain management index") OR INDEXTERMS("palliative nursing"))
AND
(INDEXTERMS ("Home Care Services") OR INDEXTERMS("bereavement care") OR INDEXTERMS("Hospice Care") OR INDEXTERMS("Hospices") OR INDEXTERMS("Palliative Care") OR INDEXTERMS("palliative therapy") OR INDEXTERMS("Respite Care") OR

INDEXTERMS("supportive care") OR INDEXTERMS("terminal care") OR TITLE-ABS-KEY ("Bereavement care") OR TITLE-ABS-KEY ("home hospice") OR TITLE-ABS-KEY ("Hospices") OR TITLE-ABS-KEY("Home Care Services") OR TITLE-ABS-KEY("Palliative Care") OR TITLE-ABS-KEY("Respite Care") OR TITLE-ABS-KEY("supportive care"))

IV. Inclusion/exclusion criteria

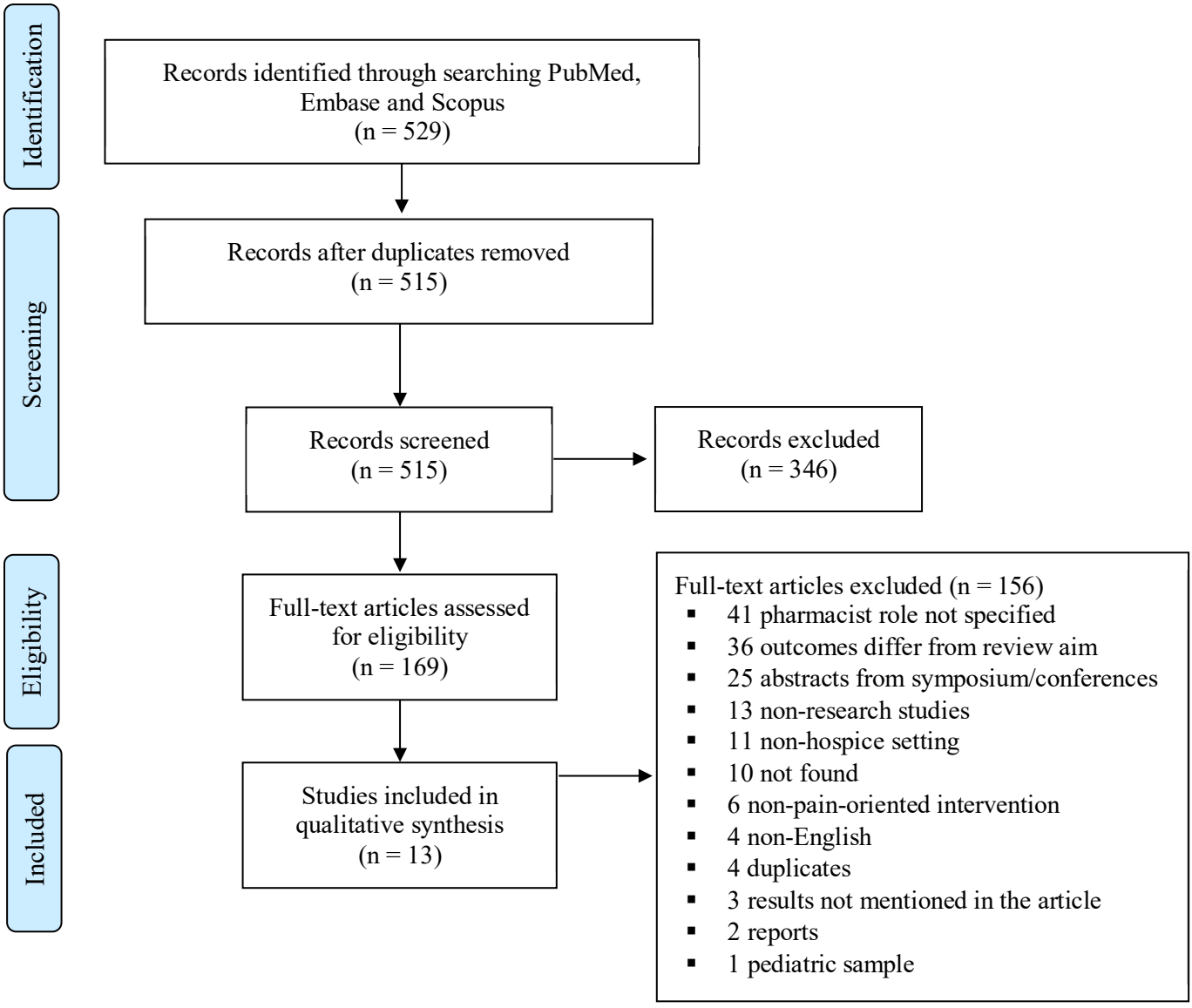
All studies published in English between January 2010 to January 2019 were evaluated in the systematic review. Included articles described studies that evaluated the treatment for pain (chronic, cancer, neuralgia, visceral etc.) in the hospice and/or palliative care setting (e.g. routine home, continuous home, general inpatient, respite care). Furthermore, the studies were required to detail the pharmacist role in hospice/palliative care pain management, either alone or as a part of a multidisciplinary team. Finally, the study was required to report some form of measurable outcome, either from a clinical or cost perspective, such as recommendations, modifications to medication dosage, reduction in adverse events, value of pharmacist, etc. Articles focused on pediatric hospice/palliative care were excluded from the study, and medical conditions other than pain for which outcomes were evaluated were not discussed.

V. Data extraction

The compiled included citations were imported in a reference manager, EndNote X8 (Clarivate Analytics; Philadelphia, PA). There were total 702 articles which were scanned for duplicates. A total of 515 articles remained after removal of the duplicates, carried forward for title/abstract screening and full text review in a systematic review manager, Covidence (Melbourne, Australia). The full text for the articles was searched and downloaded online; in case of non-availability, they were requested through the Duquesne University interlibrary loan service. One reviewer was involved in assessing the eligibility of the articles throughout the systematic review. In case of any ambiguity, it was resolved through discussion between thesis advisor and the reviewer.

The PRISMA diagram showing the search strategy is shown in **Figure 1.**

Figure 1. PRISMA chart



Further definitions of reasons for exclusion: (1) pharmacist role not specified: study did not include pharmacist involvement in pain management, (2) outcomes differ from the review: study did not detail measurable clinical/economic outcomes, (3) non-research studies: descriptive analysis only without research intervention, (4) not found: full texts were not available via online/inter-library loan, (5) duplicates: articles previously failed to be excluded in duplicate removal procedure, (6) reports: official announcements

VI. Results

A total of 169 full texts were scanned for inclusion, with **Figure 1** describing the reasons for exclusion. Finally, a total of 13 articles were finalized for qualitative synthesis. Of all these articles, six were conducted in the US,[51,52,55-58] two in Japan[59,60] and other countries (one each in China,[61] Poland,[62] UK,[63] Qatar,[64] and Korea[65]).

VII. Extraction

Table 1 gives an overview of included studies, regarding the setting, pharmacist role, outcomes assessment, study sample, key findings, and limitations. Out of the 13 studies, seven (54%) prospectively evaluated the impact of a clinical pharmacist on patient pain control. Four studies (31%) retrospectively evaluated a pharmacist-led intervention in hospice and palliative care and two studies (15%) conducted survey research among pharmacist/hospital staff to understand pharmacist's contribution to hospice and palliative care.

Table 1. Extraction results of the studies

Author Year Country	Study Aim	Study Design	Patient/study sample	Pharmacist role	Results
Atayee[56] 2018 (US)	Describe an inpatient palliative care pharmacist's interventions and outcomes; Evaluate the impact on length of stay (LOS), length from admission to palliative care consult (LTC), and time from consult to discharge and death (CTD).	Retrospective study of patients under part-time palliative care clinical pharmacist care as part of a consultation team	Hospitalized patients seen by pharmacist September 1, 2015, and March 30, 2017.	(1) guiding the transdisciplinary team on medication selection, dosing adjustments and titrations, (2) educating on medications, importance of adherence, symptoms, (3) recommending changes to medication orders, labs, and diagnostic testing, (4) serving as liaison between the palliative care team and the department of pharmacy, (5) providing home medication supply at discharge, and (6) follow up communication with the outpatient palliative care team.	Pharmacist involvement resulted in a significant difference in pain consultation and days from consult to discharge VS to the patients seen by the palliative are team. In total, patients received an average of 3.5 interventions and 4.1 documented outcomes. Most common interventions and outcomes: optimized symptom drug regimen (92.75%), education of patient/provider (90%) and change in med therapy implemented (90%), healthcare professionals educated (84.5%). There was a significant difference between patients seen by pharmacist VS palliative team for: consultation of pain (80.9% vs 39.4%, $p<0.005$). Comparison based on pharmacist visit time within 3 days of hospitalization VS 3 or more days after hospitalization: LOS (10 VS 25, $p<0.005$), LTC (3.79 VS 9.48, $p<0.05$), and CTD (6.1 VS 14.59, $p<0.005$).

Chen[61] 2014 (China)	Compare the effectiveness of opioid treatment between cancer patients receiving interventions from Clinical Pharmacist Led Guidance team (CPGTs) and a comparable control group.	Prospective, multicenter, double armed controlled cohort study	18 years or older, diagnosed with cancer pain by an oncologist, and able to receive opioid treatment for more than two weeks. Patients previously treated with opioids were also included	(1) physician and patient education, drug-use monitoring, evaluation of drug responses, (2) consultation in cases of pain or in case of complications (without prescribing), (3) monitoring drug efficacy and toxicity (follow-up)	Outcomes for standardization of opioid administration broadly improved through the use of the CPGT intervention, including more frequent pain assessments before therapy (OR:3.39 [2.78-4.14]), dose titrations before SR formulations (OR: 8.12 [6.34-10.78]) and dosage increases (OR: 9.67 [8.11-11.02]). Fewer inappropriate prescriptions and conversions were utilized, while SR formulation use increased. CPGT resulted in better pain control (scale 1-10) by site (bone [3.1 vs. 4.2, P=0.038], body [1.2 vs. 3.6, P=0.041], visceral [1.9 vs. 3.1, P=0.024), nerve [2.7 vs. 4.8, P=0.045]) and improved QOL (48.3 vs. 37.6, P=0.032, scale 0-60). Adverse events were significantly reduced in the CPGT group for constipation, nausea, and vomiting.
Edwards[63] 2019 (UK)	Determine whether medicines consultations for patients with advanced cancer pain are feasible and acceptable.	Prospective, multicenter study. Patients with cancer received consultation regarding medication use from the pharmacist along with baseline and post consultation questionnaires.	Patients with advanced cancer pain between November 2015 and March 2017 aged 16 years or older, aware of their diagnosis, on a prescribed opioid, not on any anticipatory medicines for end-of-life care and with capacity to provide informed consent and complete questionnaires.	Provide medicine consultation and recommendations to the patients, identify drug-related problems, and provide intervention	A mean of 2.5 drug-related problems per patient were identified, most commonly including effects of drug not optimal (n=25) and unclear problem/complaints (n=7). Lack of information (n=15) and non-adherence (n=16) were the main causes reported. Intervention provided for most of DRPs and their causes was patient counselling (n=35). The intervention has a positive impact on the mean pain score pre vs post consultation (4.1 vs 4.0).

Geum[65] 2019 (Korea)	Evaluate the impact on pain management by multidisciplinary palliative care team (mPCT) and the team pharmacist.	Retrospective analysis of the medical chart review. Patient reported pain intensity was recorded three times: (1) seven days before palliative care unit (PCU) admission (day -7), (2) on the day of admission (day 0), and (3) seven days after admission (day 7)	18 years or older, hospitalized for 7+ days between April 2014 and December 2015, after being transferred from the wards, emergency center, or outpatient clinics due to worsening of oncologic pain.	(1) recommending medications and evaluating analgesics, (2) validation and intervention of analgesic prescriptions based on the type and severity of pain, dose, routes, and schedule, (3) assessment of contraindications, drug interactions, and adverse effects, (4) patient counseling for nonadherent patients, (5) educating staff on evidence-based treatment with new analgesics	Mean pain intensity and appropriate use of analgesic improved gradually for patients admitted in the PCU with the mPCT. Appropriate analgesic use was higher when compared to patients who were taken care by mPCT (35.04% on day -7, 34.19% on day 0 and 75.21% on day 7) (P<0.001). Appropriate opioid use was 76.9% on day 7, 35.9% on day 0 and 35.9 on day -7 (P<0.001) and mean pain intensity score was 2.66 on day 7 of PCU and 4.05, 3.16 on day 0 and day -7, respectively. Decrease in inappropriate use of opioid was observed on PCU admissions. As per the Korean Cancer pain management guidelines, appropriateness of analgesic doses (for chronic pain: 87.2%, 80.3%, and 95.7% on day 7, day 0, and day 7, respectively; P= 003; for breakthrough pain: 88.9%, 88.9%, and 96.6% on day 7, day 0, and day 7, respectively; P=0.049) and the rate of reassessment of each patient's pain to adjust the medication for breakthrough pain (63.2%, 68.4%, 91.5% on day 7, day 0, day 7, P<0.001) both significantly improved over time.

Ise[60] 2014 (Japan)	Examine the clinical, educational and research activities of pharmacist in a palliative care team, their perceived contribution to the team or why they do not contribute.	Multicenter, prospective study using questionnaires mailed to pharmacists in cancer hospitals across the country	Pharmacists working in the palliative care for cancer patients from November 2012 to January 2013.	(1) ward rounds, counselling patients, managing adverse drug effects, drug interactions, strategies for titration and rotation of drugs, provided information/suggestions about the efficacy, adverse effects, and interactions of drugs used to alleviate symptoms, informed the primary pharmacists about patient pharmacotherapy requests, (2) education and research activity of palliative care: organizing conferences, presenting research work.	Clinical activity provided by pharmacist were direct counselling of the patients regarding opioids (29%) and adverse effects due to opioids (19%). As a part of the palliative care team they provided suggestions to the team regarding managing adverse effects of opioids (35%), rotation of opioids (34%), pharmacology of opioids (34%), drug interaction of opioids (33%) and managing adverse effects of opioids (21%), pharmaceutical production of opioids (21%). Pharmacist are most commonly involved in providing suggestion to team's primary pharmacist sometimes (35%) and often/always (24%), 70% pharmacist agreed on some level of contribution to the palliative care team, 16% reported they could not contribute and main perceived reasons for no contribution were insufficient time (90%) and/or staff (68%).
Ma[58] 2016 (US)	Evaluate pharmacist interventions and patient outcomes of a pharmacist-led outpatient palliative care practice.	Single-center, retrospective analysis of medical records conducted at cancer center with a transdisciplinary clinic with two pharmacists.	18 years or older, with a diagnosis of cancer between March 2011-2012.	(1) assess, initiate, stop, and or adjust therapy for the management of pain, nausea/vomiting, under physician direction, (2) optimize medication therapy, (3) compose clinical encounter and documented recommendations for therapy in the electronic medical record, (4) schedule follow-up visits to monitor symptoms and medication use.	Patients with severe pain (48%) showed gradual decrease in pain over the four visits. More patients (64%) were found in the stable pain state by the end of the four visits. Pain medication problems identified by the pharmacist included lack of efficacy, nausea, vomiting decreased with increase number of patient visits to the setting. Majority of patients (61%) were assigned a change in the opioid dosage as an intervention.

Mancini[55] 2012 (US)	Describe the operational aspects of multidisciplinary supportive oncology clinic.	Prospective, multicenter study of pharmacist assessments as part of the clinic regarding drug interaction, duplication in therapy, lack of efficacy and untreated condition.	Oncology patients referred to the clinic for early palliative care based on National Comprehensive Cancer Network (NCCN) guidelines.	Prior to visit: evaluation of medication list; check for drug interaction; assess for duplication therapy; form a patient-friendly medication list On the day of visit: reviewing patient's medication containers; assess for drug interaction, adverse effects, adverse effects and untreated conditions; provide recommendations and consultation service After visit: provides recommendations to team regarding medication changes, provides updated medication list , fill out the assessment, providing consultation	The results of the assessment were reported as follows: (1) Access to medication: higher cost (53.5%), transportation issues (20%), lack healthcare access (32%), (2) adherence to medication: missing at least one dose (62.7%), (3) medication therapy review: most common problems were duplication of therapy (46.7%) for breakthrough of sleep (25.6%) and pain (20.5%), drug interaction (44%) with the majority due to warfarin (24.3%) and metoclopramide (21.6%), side effects (74.7%) with most common being constipation (27.9%), lack of efficiency of drugs (94.7%) mostly the drug used for pain (31.9%), and untreated conditions (73.3%) such as fatigue (25.5%) and constipation (12.7%). Positive feedback was acquired from the patient for involvement of a pharmacist in their pain management.

Naidu[57] 2018 (US)	Evaluate pharmacist-initiated interventions and validate the pharmacist's role on a transdisciplinary palliative care team at a community hospital.	Single center, retrospective analysis of medical records related to patient interactions with a palliative care pharmacist.	Patients who had a palliative care consult order and a pharmacist-generated clinical note in the medical record between November 1, 2013 and October 31, 2014.	(1) participate in palliative care team rounds three times each week; (2) contribute to management plan for all patients with symptom issues; (3) providing medication education to patients, families, and staff; (4) coordinating interventions for pharmacy-related issues with discharge planners and physicians; (5) participating in family meetings with physicians and other palliative care team members; (6) initiate and adjust opioid doses, including transitions from parenteral to oral agents, and participate in pain and dyspnea management for end of life care patients.	Pharmacist intervention resulted in reduction (4.6 to 2.0) of pain score in acute and chronic pain suffers (5.7 to 2.5 points). Patients with interventions for moderate to severe signs of symptoms showed improvement in their condition; nausea 42/44 (95.4%), dyspnea 82/92 (89%) and anxiety 39/45 (86%), Pharmacist participated in family meeting (n=142), completed a total of 58 advance care directories and forms. A considerable cost saving was observed through direct cost reduction of $100,000 due to treatment discontinuation initiated by the palliative care pharmacist.

Pawłowska[62] 2015 (Poland)	To provide an overview of the current state of pharmacy practice at Polish residential hospices.	Cross-sectional survey with three types of questionnaires addressed to pharmacists, hospice directors and hospice physicians.	Pharmacists, hospice directors and hospice physicians at 93 residential hospices identified through a web database in 2012.	(1) the most common service provided by the pharmacists was providing advices on drugs and medical devices (75%) followed by various other responsibilities such as dispensing of drugs and medical devices, co-participation in therapy management, participating in rationalizing of drug therapy and monitoring adverse reactions, (2) as per the hospice directors expected role of pharmacist was participation in clinical trials and training hospice care staff, preparing sterile drug formulations, preparing enteral feeding solutions and compounding drugs, (3) other roles such as advise members of the therapeutic team, providing opinions to physicians, advise on pharmacotherapy choices.	Ten (63%) pharmacists estimated their involvement in this service at a level of 100%. The hospice directors and physicians indicated the necessity for including the pharmacist within the therapeutic team more frequently than respondents employed at hospices where there was no pharmacist contribution (p=0.02480 and 0.003, respectively). There was no statistically significant difference between the opinions of in the three groups of respondents regarding the benefits associated with providing pharmaceutical services at a hospice except for better selection of drugs for individual patients was indicated more often by hospice pharmacists than hospice directors (p=0.03) and physicians (p=0.02). Majority of the opinions regarding benefits employing pharmacist in hospice care were improved access, decrease cost of the pharmacotherapy, and proper drug storage.

Richter[51] 2018 (US)	Investigate clinical and financial impacts of adding a clinical pharmacist to the hospice care team	Prospective, single-center study. A clinical pharmacist was added to the interdisciplinary group (IDG)	Hospice care patients, comparing 2016 (pre) and 2017 (post) data	(1) attend IDG meetings, (2) formulary management and adherence for hospice patients, (3) chair for the P&T committee, (4) prevention of controlled substance diversion, (5) education of clinical staff, (6) general drug reference for physicians and nurses, (7) consultation, (8) present emerging trends in drug therapy for hospice patients.	Financial impact: As per the time spent in the IDG meeting and its preparation, value of pharmacist was about $138 per hour. Average PPD drug cost decreased from $5.44 to $4.07, resulting in direct drug cost saving of $329,797 from baseline and cost benefit per intervention per month of $72.52. Total cost saving was $427,705 including indirect cost saving ($15,750) and outside consultant pharmacist ($60,000). Clinical impact: Major impacts in reducing unnecessary medications on the patient's medication list, improving medication use during drug shortages and eliminating medicine increasing fall risk in patients.
Valgus[52] 2010 (US)	Describe a pharmacist-led, interdisciplinary method of care delivery begun at the University of North Carolina; describe the characteristics of the population seen and the role of the individual members of the interdisciplinary team, and provide an early analysis of the program's impact on symptom improvement	Prospective analysis and retrospective medical chart review for studying the impact of a pharmacist led multi-disciplinary team for supportive care in cancer patients	Adult cancer clinics: radiation, surgical, gynecologic, hematology, and medical	Clinical pharmacist practitioner approved to provide drug therapy management under physician direction. Two delivery models: (1) consult service, with care provided at clinic where patient already seen, and (2) structured visits at separate clinic with initial assessment (cognitive/medication) by pharmacist. Encounters studied included consultation by nurse/pharmacist (28.6%) or nurse/pharmacist/physician (22.7%); 10.3% included pharmacist consultation alone	Across first 18 months of service, patient volume and encounters increased from 4.5 to 6.6 per month, and 13 to 20 per month, respectively. Among a subset of 54 patients assessed on pain medication, encounters with the service resulted in 40% of patients receiving an increased dose, 23% receiving a new medication, 15% switched to another opioid, and 15% with no change; methadone was the most common addition/switch. Among a subset of 49 patients assessed, reductions in symptom scores for pain, nausea and constipation decreased and maintained across three visits.

Wilby[64] 2014 (Qatar)	Create a baseline inventory of clinical pharmacy interventions after establishment of an academic cross-appointment in palliative care and to assess the perceived importance of interventions made.	Prospective, single-center characterization study. Data collected included: (1) number of patients admitted to palliative care while study pharmacists were on service, (2) actual or potential drug therapy problem, (3) clinical pharmacist intervention for resolution of identified drug therapy problem, and (4) acceptance by the prescriber, if applicable. Responses of an online survey from the pharmacist in Qatar and Canada were compared for assessing importance of each type of recommendation.	Palliative care service between September 1, 2013 and December 1, 2013. Additional data was also collected via pharmacist survey.	(1) identifying actual or potential drug therapy problem (2) assignment of an intervention/recommendation for the identified problem (3) ranking of the perceived importance of each of the recommendation given by study pharmacists	32 patients were seen (the average intervention rate of 3.0 per intervention per patient). On removal of education-related interventions, 81% of pharmacist's recommendations were accepted by physicians. Discontinuation of drug therapy (29%) and initiation of drug therapy (25%) recommendations were most common while referral to other professionals (2%) was least common. A significant difference existed between overall rankings for each question between pharmacists in Canada and Qatar ($p<0.05$). Initiation of drug therapy (10) ($p=0.955$), discounting of drug therapy (10) ($p=0.758$) and, physician/nurse education (10) ($p=0.918$) were among highly rated interventions/recommendations among the pharmacists from Qatar and Canada.

Yamada[59] 2018 (Japan)	Evaluate the effect of continuous interventions for pain management and opioid-induced side effects in outpatients with cancer.	Single-center, prospective study. Four pharmacist interviewed patients from the first visit for opioid introduction to interventions via telephone to assess pain patterns, doses, side effects, and recommendation acceptance rates.	Outpatients administered opioid treatments for cancer pain relief and who received pharmacist interventions from October 2014 to March 2016.	(1) introduction to opioids at the first visit, (2) interventions through telephonic interviews between 3-7 days of first visit, (3) daily patient counseling, (4) training patient to assess pain intensity and pain response to analgesics, how to treat breakthrough pain using rescue doses, and how to prevent or treat side effects caused by analgesics, (5) increasing opioid doses or administering alternative opioids was recommended to the physicians in case of need for titration of analgesic preparation for pain control, (6) recommended adequate antiemetic or laxative drugs for symptom management	Pain intensity decreased gradually along with increase of visits (occasion) with the pharmacists. A significant change in the worst, average, and least pain scores at visits 2 and 3 compared with those at occasion 1 ($p<0.001$). Side effects scores showed a significant difference only between visit 1 and 3 (n=18, $p=0.030$). Pharmacist provided 48 new recommendations with an acceptance rate of 85.4%; maximum accepted (21/25) recommendations were change of dose (n=25) out of which (n=20) there were dose changes for opioids.

CPGT- clinical pharmacist-led guidance team, CTD- time from consult to discharge and death, DRPs- drug related problems, IDG- interdisciplinary group, LOS- length of stay, LTC- length from admission to palliative care consult, mPCT- multidisciplinary palliative care team, NCCN- National Comprehensive Cancer Network guideline, OR- odds ratio, PCU- palliative care unit, PPD- per patient day, QOL- quality of life, SR- sustained release.

a. Prospective evaluations of pharmacist-led interventions

These seven identified studies contain an intervention led by a pharmacist or detail a pharmacist involved in the hospice and/or palliative care of patients. Outcomes of administered interventions were assessed by evaluating pain intensity. Six out of the seven studies focused on the management of pain among patients with cancer in a hospital/clinic setting[51,52,55,61,63,64] and one study was conducted in an outpatient setting.[59]

A study by Chen et al[61] compared the effectiveness of opioid treatment between patients with cancer receiving care from a clinical pharmacist-led guidance team (CPGT) and a control group. One of the important pharmacist roles within the CPGT was evaluation of pain and follow-up with patients. Pharmacists were involved in selecting drug therapy for patients along with physicians. The procedures included in selection of drug therapy were initial pain assessment, dose conversion, selection and titration, all of which were referred to as process parameters. Similarly, outcome parameters contained results of pain evaluation before and after medication administration, occurrence of adverse events and quality of life measurements. Pharmacists collaborated with nurses in following up regarding management of adverse effects. The effect of a clinical pharmacist in the CPGT group was assessed for both the process and outcome parameters. Results from the study show that there was a higher rate of accurate assessment of pain severity in the CPGT group (97.4% vs 71.8%, $p<0.001$). Process parameters such as standardized dose titration, changes in specific opioids and errors in dose conversion improved significantly in the CPGT group vs control group ($p<0.001$). The pain scores assessed using a numerical/visual scale for the CPGT group demonstrated better control for bone pain (3.1 vs. 4.2, $p=0.038$), body pain (1.2 vs. 3.6, $p=0.041$), visceral pain (1.9 vs. 3.1, $p=0.024$), and nerve pain (2.7 vs. 4.8, $p=0.045$). The rates of adverse events among the patients in the CPGT intervention group were lower than the control group, with a significant difference in rates of constipation, nausea, and vomiting ($p=0.041$, 0.028, 0.035). Further, quality of life (QOL; on a scale from 0-60) scores in the CPGT group were found to be better compared to the control group (48.3 vs 37.6, $p=0.032$).

Mancini[55] evaluated the value of adding a part-time pharmacist for the palliative care of patients with cancer. The service provided by the pharmacist was distributed among pre-visit, visit and follow-up services. Before the visit, the pharmacist evaluated the medication list of the patients from the electronic medical records and checked for drug interactions and

duplications of therapy. During the visit, in coordination with the nurse, the pharmacist went through the medication list and discussed any difficulties with adherence, making recommendations when necessary. After the visit, the pharmacist guided the team regarding changes in drug therapy for the patient, if applicable, and filled out the assessment. The pharmacists under nurse practitioner's guidance made necessary medication recommendations. The assessment evaluated five areas of medication management, including: (1) medication adherence, (2) access to medication, (3) continuity of care, (4) medication reconciliation, and (5) education. Patients reported various concerns regarding access including cost issues (n=40, 53.5%), transportation costs (n=15, 20%), and access to healthcare (n=24, 34%). The medication therapy review of the patients allowed the pharmacists to go through drug interactions, adverse effects, lack of drug efficacy and untreated conditions. The results showed most common duplication therapies included sleeping meds (n=9, 25.6%) and breakthrough pain meds (n=4, 26.5%), side effects included constipation (n=16, 27.9%), and lack of efficacy in controlling pain (n=23, 31.9%). The most common untreated condition found during the assessment was fatigue (n=14, 25.5%).

Valgus et al[52] evaluated the integration of a pharmacist in ambulatory care for an oncology supportive service on a team with a nurse and a physician. Typically, a structured visit was arranged for patients on acquiring approval from the primary oncologist. An initial cognitive assessment and detailed medication history review was conducted by the pharmacist, and then physicians and nurses went through a detailed symptoms management assessment. Finally, a team meeting was held for discussing treatment recommendations, medication changes, symptoms interventions or any referral services to be provided to the patient. The collected data included demographics, symptoms scores (scored on a scale from 1=no pain to 5=most severe) and medication for symptoms (pain, nausea, vomiting and constipation). Based on referral encounter data from a total of 292 patients, 30 (10.3%) patients were consulted alone by the pharmacist, and in 99 (34%) encounters, the pharmacist worked as a team with physician/nurse. Out of total 89 patients, 88 (75%) visited the outpatient service for pain management. Out of total 54 patients with pain, 52 (96.29%) were taking either methadone or another long-acting opioid. After the initial visit, it was found that 40% of the patients had increases in their medication doses, 23% had a new medication added, and 15% switched to other opioids or had methadone started as a new therapy. The initial analysis of records of first

49 patients showed an improvement in the mean symptoms scores of pain management across the three visits evaluated, although this was not statistically evaluated.

Richter[51] studied the clinical and financial impacts of adding a clinical pharmacist in the hospice care interdisciplinary group (IDG). The clinical pharmacist carried out functions such as preventing controlled substance diversion, attending IDG meetings, educating other clinical staff, consulting pharmacist of the care centers, promoting formulary management and adherence. The financial benefits showed a decrease in per patient drug (PPD) cost from 2016 to 2017 from $5.44 to $4.07 and a direct drug cost savings from the interventions made in the IDG meeting of $329,729. The month-to-month intervention cost saving was estimated at $75.52. Interventions not made during the IDG meeting demonstrated savings of approximately $22,189. Overall, there was decrease in number of emergency visits and patient falls. Overall, including a clinical pharmacist in the hospice care team benefited by saving $427,705 annually. In terms of clinical functions, the clinical pharmacist was involved in patient consultation and accompanying physicians or nurses during patient visits. This assisted in patient education regarding medication use, exploring alternative medication options in case of lack of access to drugs and reducing use of unnecessary medications. The major clinical and financial impact of the clinical pharmacist was through their involvement in optimizing therapy regimens for patients and formulary management. The pharmacists consulted patients on topics such as drug dosing and selection strategies in a variety of settings from inpatient care centers to the patient's home. Overall, there was a positive impact of adding the pharmacist to the clinical team as formulary adherence and accuracy was observed in the medical lists of the patients.

Yamada et al[59] explored a pharmacist-led intervention for pain management among patients with cancer within an outpatient clinic setting. The intervention was provided before the physician visit and during every follow-up visit. The service involved patient counseling through face-to-face interviews and telephone. During the session, patients were taught how to assess pain intensity and response to analgesics, how to treat breakthrough pain using rescue doses, and how to prevent or treat side effects caused by analgesics. A gradual decrease of the proportion of patients reporting severe pain after pharmacist intervention occurred across visits: 15/26 (51.7%), 10/27 (37.0%), 7/24 (29.2%), 4/14 (28.6%), 1/5 (20.0%), and 1/5 (20.0%), on visits one to six, respectively. Apart from this, the pharmacist also made

recommendations regarding change of dose, introduction of new medications and termination of existing medication if necessary. Out of 48 total recommendations made, 41 (85.4%) were accepted by the physicians.

Edward et al[63] evaluated the feasibility and acceptability of pharmacist-delivered medicine consultation for patients with cancer. Community pharmacists were directly accessible by the patients in case of emergency or untreatable conditions, and the study quantified drug-related problems and the recommendations provided by the pharmacists. The pharmacists carried out telephonic or face-to-face medication utilization reviews (MUR), followed by patient and pharmacist feedback regarding change in intensity of pain before and after the consultation (on a scale of 0=no pain to 10=pain as bad as they could imagine). In total, 47 drug-related problems were identified in 17 patients with a mean of 2.5 per patient. The problems were classified based on Pharmaceutical Care Network Europe Foundation (PCNE) classification. The most common drug-related problem encountered during the consultation was pain due to reasons such as no effect of drug treatment (P1.1) (n=1, 7%), effect of drug treatment not optimal (P1.2) (n=12, 80%) or result of untreated symptoms (P1.3) (n=3, 13%). The most common cause was lack of information regarding side effects of the drug (C7.1) (n=6/15, 40%) and advice (C5.2) (n=8/16, 50%). The most common intervention provided for the common drug related problems was patient counseling for pain (I2.1) (n=12/35, 34%). The post-consultation pain score was found to be improved over that of the pre-consultation pain score (mean: 3.45 vs 3.95, p-value not specified). The telephonic consultation found to be highly acceptable amongst the patients and healthcare professionals.

Wilby et al[64] described the modernization that took place in the palliative care setting in Qatar as a part of National Care Strategy. Clinical pharmacists were added as a core component of the palliative care multidisciplinary team. The pharmacist underwent academic cross-appointment training which was accredited by Canadian Council of Accreditation of Pharmacy Programs (CAPP). Along with enrollment in a clinical program, they worked in a palliative care setting. An inventory list of recommendations was made based on consultation provided by these cross-appointed pharmacists. The perceived importance of these recommendations was ranked by both the pharmacists in Canada and Qatar (on a scale of 1=lowest importance to 10=highest importance). The recommendations list most frequently identified discontinuation of drug therapy (29%) and initiation of drug therapy (25%). There was no

significant difference found between overall rankings for each question between pharmacists in Canada and Qatar ($p>0.05$). The perceived importance of the interventions between the pharmacist at Qatar and Canada was as follows: initiation of drug therapy (10, $p=0.955$), discounting of drug therapy (10, $p=0.758$) and, physician/nurse education (10, $p=0.918$). The study provides a strong rationale of adding a clinical pharmacist in a palliative care setting as an evidence of the services they can offer.

b. Retrospective evaluations of pharmacist impact

Atayee et al[56] described the outcomes associated with adding a clinical pharmacist to a palliative care service in an inpatient setting. The study retrospectively assessed hospitalized patients evaluated by a specialist palliative pharmacist at University of California, San Diego. The analysis focused on identifying the inpatient pharmacist interventions provided to the patients, as well as evaluating the outcomes related to the interventions provided as a part of the primary assessment. The study also evaluated length of hospital stay (LOS), reason for consult to palliative care team, length from admission to palliative care consult (LTC), and time from consult to discharge or death (CTD) of the patients. In the inpatient setting, pharmacists were involved in educating/training other team members and patient family members, dose changing, and medication selection. Pharmacists served as liaisons between the palliative care team and the department of pharmacy at the medical center. The most common documented intervention and outcome found were optimizing palliative care medications ($n=371$, 92.75%) and change in the medical therapy implemented ($n=300$, 90%). Early exposure of clinical pharmacists to the patients (i.e. within >3 days of hospitalization) was found to improve LOS, LTC and CTD (10, 3.79 and 6.09) compared to exposure after >3 days of hospitalization wherein LOS, LTD and CTD was 24 ($p=0.00004$) , 9.48 ($p=0.013$) and 14.59 ($p=0.000009$).

Naidu[57] assessed the role of a palliative care pharmacist in a community hospital. Pharmacist responsibilities include participating in team rounds, forming symptom management plans, educating staff and family members, coordinating pharmacy related interventions, and completing Physician Orders for Life Sustaining Treatment (POLST) forms. Alongside physicians, pharmacists were able to initiate, adjust or transition medications as per patient pain relief requirements. A retrospective cohort study was conducted and evaluated medical records of patients who had palliative consult orders and a clinical note from a pharmacist in

their clinical record. The data included patient's pain scores (on scale of 1 to 10) before and after 24 hours, of intervention administered. A reduction in pain score from 4.6 to 2.0 points was seen among acute pain patients (n=125, 47%) and 5.7 to 2.5 in chronic pain (n=140, 57%) patients after administration of pharmacist intervention. Out of the total patients who stated a numerical pain value (n=191), 174 (91%) met their pain goal within 24 hours. In case of symptom management, nausea and anxiety scores were improved post-intervention. The most common interventions provided by the pharmacist were education, counseling patients and making proper medications available for them. The pharmacist service had a positive financial impact due to discontinuation of unnecessary medications, tests, or procedures. Palliative pharmacists achieved a direct cost reduction of $1000 due to treatment discontinuation. In line with published literature, a reduction in cost per day of $279 for patients discharged alive and $374 for patients who died as inpatients was achieved through the consultation program.

Ma et al[58] described the role of pharmacist on a palliative care team in an outpatient setting, providing consultation during visits for pain management and involved in documentation and interventions on medication problems. Advanced care planning was provided to assess, initiate, stop, and/or adjust therapy for the management of pain, nausea/vomiting, and other symptoms due to lack of efficacy, adverse effects, nonadherence or missed doses, drug interactions, evaluating duplications in therapy and providing recommendations regarding medications. All patients assessed by the palliative care pharmacists were included in the study, with their pain (on a scale of 1-10) scored as mild (1-3), moderate (4-5) or severe (6-10). During the first visit (n=80), 38 (48%) were classified with severe pain, and at the second visit (n=59), 21 (36%) reported improvement in pain. At third (n=43) and fourth visits (n=33), the number of patients with stable pain were consistent (21 [49%] and 14 [42%]). All the pharmacists identified constipation as an adverse effect in the subsequent visit and the most common intervention provided was starting a new medication.

Geum et al[65] explored the impact of a multidisciplinary palliative care team (mPCT) and pharmacist on pain management. Data from medical records of the patients admitted in the palliative care unit (PCU) was retrospectively collected. The mPCT team, along with the pharmacist, conducted medical rounds collecting information regarding pain severity and other symptoms. The pain intensity (scored on a scale of 0 to 10) was documented seven days before PCU admission (day -7), on the PCU admission day (day 0), and seven days after the PCU

admission (day 7). Pharmacists were involved in providing medical therapy recommendations and evaluating use of analgesics. The analgesic use followed the Korean Cancer Pain Management Guidelines and the National Comprehensive Cancer Network (NCCN) guidelines. A medication was deemed eligible for use if it satisfied all six categories of recommendations within the guideline, including: (1) drug selection based on the type and severity of the pain, (2) dosage for chronic pain, (3) for breakthrough pain, (4) reassessing each patient's pain to adjust the pain medication to meet the patient-specific goals for comfort, function, and safety, (5) analgesic use that reflects renal or hepatic function, and (6) monitoring adverse effects. The results of the study showed that pain scores were worst on day 0 (4.05), compared to day -7 (3.16) and day 7 (2.66). The appropriateness of analgesic used improved along the days of the admission, from day -7 (35.0%), day zero (34.2%) to day 7 (5.2%) ($p<0.001$). The analgesic use as per the six categories recommendations improved over time (day -7, day 0, day 7) for chronic pain (87.2%, 80.3%, and 95.7%) ($p<0.003$), break through pain (88.9%, 88.9%, and 96.6%) ($p<0.049$) and monitoring of the side effects (65.0%, 65.8%, and 86.3%).

c. Survey questionnaires regarding pharmacists in hospice and palliative care

Ise et al[60] examined responses from palliative pharmacist surveyed regarding their understanding of their activities on the palliative care team. The pharmacists were asked questions regarding their clinical, education, and research contributions in a palliative care setting and their perception of their contribution to the service. Clinical activities were rated on a five-point Likert scale (one=rarely to five=everyday). The highlighted clinical activities identified from the responses were: (1) direct counseling of patients about opioid information (18%) and adverse events of opioids (19%), (2) provision of information to the palliative care staff about managing adverse events of opioids (21%) and pharmacology of opioids (20%), (3) attending wards (79%) and conferences (94%). Their contribution to education and research activities was measured through a yes/no question. Approximately 80% of pharmacists organized a conference in their own designated cancer hospital. The perception of pharmacist contributions to the palliative care team was assessed using a yes/no question and associated reasons were rated on five-point Likert scale (strongly agree to strongly disagree). Out of 304 pharmacists, (n=212) 70% of pharmacists rated their contribution to palliative care services as

100%. Those who did not perceive their contribution to the fullest identified a shortage of time (90%) and staff (68%) for their lacking contribution.

Pawlowska et al[62] administered a survey regarding current and future roles of clinical pharmacists and their collaborations with physicians in a residential hospice among three sets of responders: pharmacists, physicians and hospice directors. Each responder had a different set of questions to answer; the hospice directors and physicians were asked about their attitudes towards the contribution of a pharmacist in the residential hospice. Pharmacists were asked questions regarding the services they provided, their role in solving drug-related problems and making the therapy more cost-effective. The majority of the respondents supported the idea of including a pharmacist in the palliative hospice care team. Specific reasons for this as per the pharmacists were delivering cost-effective therapy, while hospice directors identified better drug management and decision-making regarding therapies as the reason. A need for advice from the pharmacist was expressed by 53% of physicians (n=16/30) on the following topics: new drugs, rationalization and cost of pharmacotherapy, reimbursement, generic drugs, availability of drugs on the pharmaceutical market, drug interactions and compounding. All the respondents thought that adding a pharmacist to the hospice team would be beneficial for proper storage of drugs (61%), decreasing cost of the therapy (57%) and improving access to the drugs (53%).

VIII. Overall summary

The breadth of studies focused on evaluating the impact of adding the clinical pharmacist on the hospice and palliative care team for pain management of patients. The outcomes of pharmacist-led interventions or pharmacist involvement in palliative care were found to be associated with better pain control among the patients.[51,52,55,59,61,63,64] The studies in the review assessed the effect of study interventions on patient's pain via evaluating pain intensity. Most commonly pain intensity was recorded utilizing a numerical pain scale throughout a patient's visit to the healthcare setting. Interventions played an important role in optimizing a patient's therapeutic regimen, identifying, and solving adverse effects related problems. Furthermore, Richter[51] mentioned financial benefits gained due to the roles carried out by a pharmacist in a palliative multidisciplinary team.

The current review also provides insights regarding clinical pharmacist's role in conducting counseling sessions, medical rounds and completing patient's health assessment forms.[56-58] It also endorses pharmacist involvement in medication changes, recommendations or intervention suggestions as a response to the symptoms experienced by the patients.[65] Ise et al[60] and Pawlowska et al[62] highlighted how pharmacists perceive their importance in the hospice and palliative care through administration of surveys.

The results of the systematic literature review provide rationale to the aim of the study to understand the extent of involvement the clinical pharmacists have in hospice and palliative care settings.

IX. Limitations

Most of the studies had data from the initial phases of service implementation, where adding the pharmacist to the multidisciplinary team was just initiated. Therefore, outcomes resulting from a well-established palliative care team are not as well detailed in the review. Moreover, the current review largely did not take into consideration effects of pharmacist involvement or pharmacist-led interventions on humanistic outcomes, such as quality of life and improved functioning. Regarding clinical setting limitations, articles based on a pharmacist's role in hospice care multidisciplinary team were comparatively fewer than palliative care setting. Furthermore, non-English studies and seminar/conference data without full text were not included; therefore, studies written in foreign languages and containing relevant data may have been left out of the review.

CHAPTER 3: METHODS

I. Phase I of the study

a. Phase aim

To identify the prevalence of clinical pharmacist recommendations for methadone upon admission to hospice/palliative care. Further, to assess the acceptance of the pharmacists' recommendations for methadone after admission to hospice/palliative care.

b. Overview

Phase I of the study was conducted in two parts of data collection. 'Instrument #1 - Pharmacist data collection tool' identified whether a recommendation for methadone was made by the pharmacist based on individual indications/contraindications of patients. 'Instrument #2 - Researcher data collection tool' was utilized to follow up the patients for evaluating whether the physicians accepted provided recommendations. Descriptive and inferential statistical analysis was performed on the data collected by the tools.

1. Rationale

The involvement of a pharmacist in the hospice and palliative care has shown improvement in pain management and optimizing other patient clinical outcomes. A study performed by Lee *et al*. documented all recommendations made by the pharmacists and their effects on the patient's clinical outcomes in a palliative care setting. Out of the 87 recommendations, 73 (84%) were accepted by physicians. The patient's clinical outcomes were positively influenced by the pharmacists' pharmacotherapeutic recommendations.[66] Another study by Wilson *et al*. demonstrates that the desired clinical outcomes were achieved when the pharmacist's recommendations were accepted by the physicians.[67]

Methadone's utilization in hospice and palliative care settings has not been optimal.[41] This has been the case despite the medication gaining popularity for its pain management attribute among the patients. The medication has been studied for use in various pain states, especially pertaining to patients with cancer pain. The indications of using methadone found from those studies were: (1) management of uncontrolled pain, (2) alternative in case of opioid allergy/opioid adverse effects, (3) management of neuropathic pain, and (4) pain refractory to other opioids.[68] Similarly, use of this treatment for pain management has various

contraindications. A clinical practice guideline on safe use of methadone suggests contraindications for using methadone including: (1) prolongation of QTc interval, (2) potential risk factors of QTc prolongation like electrolyte abnormalities, impaired liver function, etc., (3) drug-related arrythmia, (4) multiple drug-drug interactions, and (5) respiratory depression.[44] Pharmacist involvement in hospice interdisciplinary teams is highly endorsed, with medication reconciliation one of their roles and responsibilities in hospice and palliative care setting. This understanding assists in using their clinical judgment to provide methadone recommendations, keeping its indications and contraindications in mind. Therefore, the strategy of obtaining pharmacists recommendation on methadone utilization will be useful in demonstrating the medication's use in this setting. Moreover, evaluating the acceptance of these recommendations will provide information on the impact of pharmacists' recommendations in hospice and palliative care setting.

a. Study sample

The sample of patients for the first part of this study included adults (18+ years old) admitted to hospices served by DeltaCareRx. These patients were newly admitted between October 2019 to December 2019.

b. Protection of human subjects

The study did not involve any direct interactions with patients (and therefore posed minimal risk); therefore, it was granted an exemption by the IRB review. Patient information was protected by usage of anonymized study ID to identify patients on research documents, corresponding to a unique patient ID used onsite at DeltaCareRx. A master sheet matching the study ID and DeltaCareRx patient ID was accessible only by DeltaCareRx staff and remained onsite at the facility. An additional master sheet was maintained onsite to keep a record of the forms filled out by pharmacists, including the names of pharmacists and numbers of forms they were assigned (e.g. the patients they collected).

c. Developing instruments for data collection

1. Instrument #1 - Pharmacist data collection tool

Preliminary literature search aided in identification of important variables in pain management.[44,69,70] The following area were chosen to characterize and evaluate methadone recommendations for pain management: (1) demographics of the patient, (2) type of pain

(classified as nociceptive, neuropathic or both), (3) pain intensity at the admission (measured on a numerical scale 1=no pain to 10=worst pain), (4) current pain medication regimen, prescribed at the time of admission to hospice/palliative care at DeltaCareRx, (5) previous recommendations of methadone, (5) breakthrough medications used in past, (6) indications for prescribing methadone, and (7) contraindications of prescribing methadone. The list of indications and contraindications are included in **Table 1**. If the pharmacist provided a recommendation for methadone, they were requested to specify the type of recommendation, including: (1) switch to methadone as maintenance treatment, (2) addition of methadone as adjunctive/adjuvant treatment, (3) discontinue methadone previously prescribed, or (4) other. These criteria were used to develop instrument #1, available in **Appendix 1**.

Table 1. List of indications and contraindications of using methadone

Indications	Contraindications
High opioid tolerance	Clinically unstable
Refractory to other opioids	Limited prognosis (< 5 days)
Morphine allergy	Drug interactions
Severe renal impairment	QTc prolongation/structural heart disease
Neuropathic pain	Severe liver impairment
	Substance use disorder
	Use of other long-acting CNS depressants

2. Instrument #2 - Researcher data collection tool

This data collection tool was utilized to evaluate whether the patients who had recommendations for methadone were accepted or not, and to collect further data on these patients. All new admission patients from the first phase of data collection who acquired recommendations from the pharmacist were followed up by a student pharmacist. The instrument also collected additional patient information including: (1) allergies, (2) comorbidities, (3) hepatic/renal dysfunction recorded as presence or absence of these conditions or any clinical value if provided, (4) nutritional status was recorded as it, (5) pain medication history of the patient prior to admission in hospice/palliative care at DeltaCareRx, and (6) pain intensity prior to and during the admission to DeltaCareRx setting, classified on a

categorical scale moderate to severe, and (7) number of days of interval from the day of admission to the date of filling the instrument #2. This gave an idea of the number of days patients were admitted to the service. Further, if the recommendation was accepted by the physicians, questions exploring the therapeutic regimen were explored in the tool. Additional data was collected regarding which day of the week the recommendation was provided in order to understand site and staff's functionality over a week's time. Further, data on interval of days passed from the day of recommendation to implementation was collected. The alignment of the accepted dose/frequency with the pharmacist recommended dose/frequency was assessed through this tool if mentioned. A copy of instrument #2 is available in **Appendix 2**.

The instruments underwent various revisions before use for data collection. Discussions with DeltaCareRx staff helped in getting insights on availability of the information for completion of instrument #2. The revisions included additional questions related to patient's clinical characteristics. The palliative prognosis scores (PPS) of the patients at the time of admission and during completing instrument #2, it was measured on a numerical scale 0=death to 100=normal. It is used to predict patient's prognosis and survival.[71] A PPS is assigned based on patient's total bed bound time, extent of diseases, ability to carry out self-care, food intake and conscious level[72]. Morphine milligram equivalents (MME)[73] patient was on during and prior to the admission was evaluated through addition of respective questions. The MME conversion factor was used to calculate the total opioid dosage prescribed to the patients.(conversion scale included in instrument #2. **Appendix 2**). Additionally, a question exploring the day of the week when recommendation was provided was also added in the tool. This assisted in assessing facility functionality based on the days of the week.

d. Data collection process

The data collection took place from October to December 2019 at DeltaCareRx. A total of four pharmacists and a student pharmacist collected data using the tools in paper format. A researcher designed the instruments for data collection and analyzed the collected data. All newly admitted patients to DeltaCareRx care underwent their usual clinical review by pharmacists at DeltaCareRx. After this, the four pharmacists filled out instrument #1 for each patient they processed. Later in the data collection, information from instrument #1 was used for follow-up if a recommendation for methadone was rendered. The patients who had instrument #1 filled, a student pharmacist filled out instrument #2 for those patients using data

available in the DeltaCareRx system. The student pharmacist calculated MME of the medications that were administered by the patients on their individual forms. Additionally, patients provided with a methadone recommendation had the acceptance section filled on instrument #2. All paper instruments contained a top section listing the DeltaCareRx patient ID and study ID (both necessary to achieve follow-up); this section was trimmed off prior to leaving the DeltaCareRx site to ensure anonymization, and then were sent to Duquesne University for analysis. The information from both the tools was transferred to a Microsoft Excel spreadsheet.

e. Data management and statistical analysis

The data from this phase was analyzed using SPSS Statistics 25 (IBM Corp; Armonk, NY). The individualized data collected for most variables was categorized to ease analysis. Examples of these categorization is provided in **Appendix 3**. Selected variables were categorized as follows. Age was classified in two classes, < 60 and ≥ 60, for the purpose of statistical analysis. The classification was made because majority of the patients admitted in hospice care are between the age 60 and higher[5]. Classes for terminal diagnosis/indication were: (1) cancer, (2) dementia, (3) cardiovascular, (4) respiratory, (5) liver, (6) kidney, (7) neurodegenerative, and (8) other. Classes for pain medications (prior to and at the time of admission) were: (1) opioid, (2) NSAID, (3) opioid/APAP, (4) gabapentin, and (5) other. Allergies were categorized as: (1) opioid, (2) antibiotic, (3) topical, and (4) other. Comorbidities included: (1) cancer, (2) dementia, (3) cardiovascular, (4) respiratory, (5) liver, (6) kidney, (7) endocrine, (8) psychiatric, (9) gastrointestinal, (10) neurological, and (11) other. The response to nutritional status was categorized as: (1) very poor, (2) poor, (3) good, (4) fair, and (5) good. Similarly, renal, and hepatic dysfunction was categorized as: (1) yes, (2) no, or (3) not known. Recoding of string variable into numerical characters was done using the transform function on SPSS. Character string variables like sex (F=1, M=2), methadone recommendation (Y=1, N=2), acceptance of recommendation (Y=1, N=2) and type of pain (1=nociceptive, 2=neuropathic or 3=both) were recoded to numerical string.

1. Research questions

Research question 1: To identify the prevalence of clinical pharmacist recommendations and acceptance for methadone use among hospice/palliative care patients

Descriptive statistics was utilized to calculate the prevalence of the methadone recommendation provided to the patients. Additionally, demographic, and clinical characteristics was evaluated for the patient sample such as patient's mean age, height, weight, BMI, and sex. Standard deviation, median, maximum, and minimum values were calculated for these variables. Individual frequencies were measured for clinical characteristics such as hospice type, pain intensity, medications, palliative prognosis scores. Range was calculated for days from the date of admission variable. Prevalence was calculated using frequency evaluation of questions regarding (1) pharmacist recommendations, and (2) acceptance of the provided recommendations.

Research questions 2: To evaluate the differences in demographic and clinical characteristic of patients provided with a methadone recommendation and patients who were not.

Inferential statistics was utilized to evaluate the difference between the study sample recommended for methadone and patients who were not. The groups were compared using independent t-test analysis for continuous variables and Chi square test analysis for categorical variables.

II. Phase II of the study

a. Phase aim

To identify the frequency in the use and monthly expenditure of three categories of medications: pain, pulmonary and anticoagulants at various DeltaCare Rx client sites. The use of the medications was stratified as per the therapeutic class of their medication category and sex of the patient across a pharmacy claims database.

b. Overview

Medication utilization data for six months (January, June, July, September, October and November) of the year 2019 was obtained from DeltaCareRx. The data consist of month wise prescription drug information, including date of claim, drug names, quantity, cost, days of supply, and patient sex. Frequency in use, total expenditure and monthly average cost was calculated for each therapeutic class belonging to the three medication categories.

The data was stratified based on the different therapeutic class and patient's sex. The total cost for each stratified subgroup was calculated. Additionally, consumption of each medication from the medication categories of interest were retrospectively evaluated from the database.

c. Rationale

Hospice and palliative care providers are assisted by DeltaCareRx in cost containment. DeltaCareRx uses a unique Rx purchasing model to achieve this for their clients. They obtain the medications from the pharmacy at highly discounted rates and provide them to their client with transparency in their pricing. The prescription drug data is generated through Deltalytics, which reports monthly utilization of medications by the hospice and palliative care providers.

DeltaCareRx staff articulated categories of interest for the analysis, including the selected three broad categories of pain, pulmonary and anticoagulants. The selection was made because of the high medication utilization and expenditure belonging to these three-medicine categories at all the hospice care sites served by DeltaCareRx .Therefore, the analysis aimed to identify the highly utilized and costly drugs from those medication categories. The evidence generated will be useful in cost/utilization optimization and developing strategies of utilizing cost effective drugs by the hospice providers served by DeltaCareRx.

d. Data source

Prescription claims data was obtained from a pharmacy benefit manager, DeltaCareRx. The organization provides services to hospice and palliative care clients. The data includes unique prescription claim of the medications dispensed to a patient at the setting.

e. Database structure

Full prescription drug data for January, June, July, September, October, November months of the year 2019 was obtained from DeltaCareRx and made available to the researcher in Microsoft Excel via multiple sheet downloads. The six months for data analysis were

selected because of availability of complete data for these months and to maintain uniformity in utilization data. These multiple sheets were merged together and named. The primary identifiers in the dataset were the prescription number and unique identification number of each patient. The data set also includes other variables such as drug name, therapeutic class (generic and standard), quantity, average wholesale price (AWP), DeltaCareRx cost, days of supply, patient sex, and denotation of new/refill medication. The variables for the study were defined as below.

The month-wise data sheets differed in content, with not all datasets inclusive of all variables.

1. **Therapeutic classification of drugs**

There were two (standard and generic) therapeutic class variables present in the data. For the present analysis, generic therapeutic classes of drugs were taken into consideration. There were 445 different generic therapeutic classes of medications utilized at different client sites of DeltaCareRx for the dataset provided.

2. **Drug names**

Drug names are the prescribed medications dispensed to hospice patients at DeltaCareRx client sites. The data includes information 3189 medications.

3. **Sex**

The data includes the sex of patients who were administered each medication. As per the information in data two nomenclatures were used to describe sex of the patients. Numerical '1' was coded for males and '2' was coded for females in some of the data sheets and others had letters 'M' and 'F' to denote sex of the patients.

4. **Generic long name**

Each drug had a generic long name provided in the data. This information was useful in segregating the drugs based on their generic names, and not the drug names, which had a

high degree of variability. For example, the generic long name, 'methadone' had various drug names in the database such as "methadone 5mg", "methadone solution 5mg/ml", "methadone con 10mg/ml".

5. DeltaCareRx medication cost

Each prescription in the database was associated with the cost charged to the patients. This was the cost charged by DeltaCareRx while dispensing the medications to the patients.

f. Utilization of medications

To assess the trends in utilization of medication of interest at DeltaCareRx client sites, a unit measurement called 'defined daily dose (DDD)' was used. The World Health Organization's definition for DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults."[74] Drug utilization data presented in DDDs gives a rough estimate of consumption of medications. Each medication has a DDD assigned as per its route of administration provided it has a designated Anatomical Therapeutic Chemical (ATC) Classification code. ATC codes classify the active ingredients of medications according to the organ or system they act on and their therapeutically, pharmacological, and chemical properties.[75] These codes are maintained by WHO Center for Drug Statistical Methodology. There are no DDDs assigned for topical products, vaccines, antineoplastic agents, allergen extracts, general and local anesthetics, and contrast media.[74] The recommendations of average maintenance doses are made depending on: (1) the recommended dose referring to a body weighing 70 kg, (2) the maintenance dose not differing from an initial dose, (3) an assignment based on the content (strength) of a product, with different salts of a product not having different DDDs, and (4) prodrugs and various dosage forms of a same drug not having been assigned a separate DDD value.

The trends in consumption of medications from three broad classes, (1) pain, (2) pulmonary and (3) anticoagulants were evaluated. A list of medications was prepared with their assigned DDD values referenced from the ATC/DDD Index 2020 website (**Appendix 4**).[76] DDD dispensed was calculated for each medication if it had the following information, (1)

quantity of medication, (2) strength of medication, and (3) DDD value. The formula for DDD dispensed used was:

$$DDD\ dispensed = Quantity\ of\ product * strength/DDD/days\ in\ month$$

g. Selection of medication categories

Researchers categorized the relevant therapeutic class of medications from the database into three medication categories. A student pharmacist reviewed the selected classes to avoid any errors in the selection process.

h. Data analysis

The frequency of each therapeutic class of medications and their cost was found from the database. Cost of each therapeutic classes was identified and compared across individual therapeutic classes. Next, all the therapeutic class in the three medication categories were stratified as per patients' sex. Cost per patients across their sex was identified for each month. SUMIF and COUNIF Excel functions were used for obtaining the stratified values as per sex of the patient and cost values. SPSS (Version 25.0) was used to carry out the descriptive statistics. The Explore function was used to calculate the mean and +/- standard deviation values of the costs of various therapeutic classes. For the purpose of this descriptive analysis, the medical categories were assigned numbers such as anticoagulant =1, pulmonary = 2 and pain = 3 for the purpose of this analysis. The dependent variables for the analysis were cost per male/female patients and independent variable was the numerical medication categories. It demonstrated the different monthly mean cost and the associated +/- standard deviation value of all the therapeutic class.

Utilization of each medications with available strength and quantity values was calculated expressed as total DDDs dispensed. SUMIF and COUNTIF functions were used across the Excel workbook to calculate the strength and quantity values. Individual DDD values of drug names were grouped under their generic long names. These values represented the sum of total DDDs dispensed.

The missing cost and quantity data in the database were filled by imputing the missing values. The missing values were substituted with the average of known cost/quantity values for the prescription. For example, in the case of missing cost value for the drug name MAPAP (acetaminophen) tablet 500 mg. The average of all the available cost values for the same tablet was substituted in the place of the missing value. In the case of missing quantity values in the database. The average of the highest and the lowest quantity value of a particular drug name was imputed for the missing value.

1. Impact of missing data

The missing values in the datasets impacted analyses in the phase II of the study. All the listed generic therapeutic classes in the table were not present in all the data of the months. Hence, those may not be uniform. The missing values of drug names and quantities did not allow for DDD calculation for those drugs. Additionally, combined products were excluded from utilization analysis because of DDD values were unavailable. The data regarding patient's sex was missing in many datasets. Therefore, the stratification analysis was not performed for that data. The quantity of missing data and its implication on the overall results is specified throughout the results of phase II.

2. Research questions

Research question 1: To identify the most frequently utilized generic therapeutic class and their expenditure from the medication categories of pain, pulmonary and anticoagulants.

Descriptive statistics was utilized to identify the values to answer the research question. The mean average cost of each therapeutic class and the standard deviation values were calculated.

Research question 2: To identify the pattern in medication utilization on the basis of sex of the patient and therapeutic class.

The difference in expenditure of various therapeutic class based on the sex of the patient was calculated for each month.

Research question 3: To identify the month wise medication consumption at DeltaCare sites.

The WHO DDD values were identified for the identified medications from the therapeutic class. Consumption values for individual medications was calculated using the dispensed DDD formula.

CHAPTER 4: RESULTS

I. Phase I of the study

a. Study aims

To assess the data collected to identify prevalence of pharmacist methadone recommendations and acceptance. Further, to evaluate the difference in the characteristics of patients provided with the recommendation vs those who were not.

b. Overview

Descriptive analysis resulted in generation of individual frequency tables of patient demographics and clinical characteristics variables. Prevalence of the provided pharmacist recommendation and accepted recommendations were calculated. The difference between the patient characteristics of patients provided with recommendations vs those who were not, analyzed using inferential statistical analysis.

c. Demographic and clinical characteristics of the sample

1. Sample size

In total, 159 instruments #1 and #2 were filled out, with 158 (99.3%) usable forms analyzed based on inclusion criteria.

2. Patient demographic variables

A total of 156 (98.7%) out of 158 newly admitted patients to the facility had their age documented on instrument #2 (**Table 2**). A total of 45 (28.5%) patients were of age between 80-89 years old, 41 (26.0%) were between 90-99 years old and 3 (1.9%) were between 100-110 years old. Patients aged 18-59 accounted for only 12 (7.6%) of the study sample. The mean age for the overall sample was 79.5 years (SD: 13.8 years). The sample had a slightly higher proportion of females (89; 56.3%) compared to males. BMI was calculated for 125 (79.1%) patients based on the available height and weight variables. From the total sample, 16 (12.8%) were classified as obese ($\geq$30 kg/m^2), 27 (17.0%) patients were overweight (25.0-29.9 kg/m^2), 64 (51.2%) had a normal BMI (18.5-24.9 kg/m^2) and 18 (14.4%) were underweight (<18.5 kg/m^2). The mean BMI for the sample was 23.7 kg/m^2.

3. Patient clinical characteristic variables

Hospice type data was collected through instrument #1. Hospice type information was included in 157 (99.3%) of the patient sample. Home hospice, for 121 (76.6%) patients, was the most utilized type reported (**Table 2**). Similarly, type of pain data was collected for 101 (63.9%) of patient sample. The majority of patients (62; 39.2%) reported having nociceptive pain. The change in palliative score was recorded from day of admission (from instrument #1) to the day of data collection (from instrument #2). The majority of values (141; 89.2%) had no difference recorded. The mean of difference of 12 was found between palliative prognosis scores pre- and post-admission scores. Overall, mean scores during the admission and after the admission were 37.20 and 37.44, respectively. The mean values of morphine milligram equivalent (MME) during the admission and after the admission were 1131.4 and 1160.3, respectively. The MME/day during the admission and after the admission was found to be 37.71 and 38.67. The data collected from the date of admission to the date of filling out the instrument ranged from 0 to 189 days.

Table 2: Demographic and clinical characteristics of hospice/palliative care patients

	n (%)	Mean (SD)
Sex Female Male	 89 (56.3) 66 (41.8)	-
Height (m)	126 (80.0)	1.6 (0.1)
Weight (kg)	133 (84.2)	65.6 (15.0)
BMI (kg per m^2)	125 (79.1)	23.7 (5.0)
Age (years) < 60 ≥ 60	 12 (7.6) 144 (91.5)	79.5 (13.8)
PPS at admission	150 (95.0)	37.2 (12.1)
PPS after admission	147 (93.0)	37.4 (12.0)
Hospice type Inpatient Assisted living Nursing home Home	 4 (2.5) 10 (6.3) 22 (13.9) 121 (76.6)	-
Pain type Neuropathic Nociceptive Both	 5 (3.2) 34 (21.5) 62 (39.2)	-
MME prior to admission	51 (32.3)	1131.4 (2261.0)
MME after admission	67 (42.4)	1160.3 (2332.5)

Age: categorization provides distribution of elderly (≥60) patients; BMI: Body Mass Index; PPS: Palliative prognosis score; MME: Morphine Milligram Equivalent; n: number of study sample reported the information; SD: Standard deviation

A total of 124 (78.5%) patients included data regarding pain intensity score at the time of admission. Most of the patients (113; 71.5%) classified their pain between the scale 1 to 6 (**Table 3**). The medications used during and prior to admission were categorized into respective therapeutic classes. In counting the number of medications patients were administering, one patient may belong to more than one medication category. The most common medication utilized in the hospice care setting was opioids (153; 97.0%) followed by APAP (55; 35.0%). Similarly, most medications in the pain medication history were opioids (122; 77.2%).

Table 3: Overall distribution of pain variables in patients before and after the admission

	n (%)
Pain intensity before admission	
Mild	68 (43.0)
Moderate	29 (18.3)
Severe	11 (7.0)
Pain intensity scores at admission	
1	21 (13.3)
2	38 (24.1)
3	16 (10.1)
4	8 (5.1)
5	18 (11.4)
6	12 (7.6)
7	5 (3.2)
8	5 (3.2)
9	1 (0.6)
Pain medication history of patients prior to admission	
Opioids	122 (77.2)
APAP	14 (9.0)
Opioid/APAP	12 (7.5)
Gabapentin	8 (5.1)
NSAIDS	2 (1.3)
Other	2 (1.3)
Pain medications at the time of admission	
Opioids	153 (97.0)
APAP	55 (35.0)
Opioid/APAP	19 (12.0)
Gabapentin	16 (10.1)
NSAID	7 (4.4)
Other	13 (8.2)

APAP: Acetaminophen; NSAID: Nonsteroidal anti-inflammatory drugs; Opioid/APAP: opioid/acetaminophen combination

In total, 95 (60.1%) of patients had their allergies documented using Instrument #2. As per the categorization, the most frequent allergy was antibiotics (47; 23.6%) followed by opioids (31; 15.3%). Although 97% of the sample was administering opioids for their treatment, alternative opioids outside of their specific allergy may have been utilized for pain management. The allergic conditions were opioid specific and alternate opioids were administrated for pain management respectively (**Table 4**). Similarly, in total 147 (93.0%) of patients had their comorbidities documented. The comorbidities were categorized as per different disease

conditions. The most common comorbidity encountered among the study sample was cardiovascular disease (116; 73.4%).

Table 4: Overall distribution of allergies and comorbidities in study sample

Allergies/comorbidities	n (%)
Allergies *	
Antibiotic	47 (30.0)
Opioid	31 (20.0)
Topical	7 (4.4)
Other	54 (34.2)
None	63 (40.0)
Comorbidities *	
Cardiovascular	116 (73.4)
Endocrine	61 (39.0)
Cancer	53 (33.5)
Respiratory	53 (33.5)
Kidney	44 (28.0)
Dementia	30 (19.0)
Psychiatric	29 (18.3)
Neurological	25 (16.0
Liver	19 (12.0)
GI	51 (32.3)
Other	73 (46.2)

GI: gastrointestinal; *one patient may be categorized in more than one class

d. Research question 1

1. Provided methadone recommendations

In total, 37 (23.4%) patients had a methadone recommendation provided by the pharmacists. The majority (26; 16.5%) of reasons of methadone recommendation was switching to methadone as the maintenance treatment. Further, other reasons included addition of methadone as adjunctive treatment (7; 4.4%) and other potential reason listed by the pharmacists (3; 1.9%).

2. Indications/contraindication of provided methadone recommendations

The recommendations provided were based on the patient's indication and/or contraindication for administering methadone. In total, 50 (31.6%) out of 158 patients had indications for recommending methadone reported. One patient may have one or more indications or

contraindications listed on the tool. The most common indication for methadone was identified as neuropathic pain (27; 17.0%) (**Table 5)**. Contraindications were documented for 68 (43.0%) patients. QTc prolongation/structural heart disease was one of the most common contraindications for methadone (38; 24.0%) (**Table 5)**.

Table 5: Indications and contraindications for using methadone in the study sample

Indications/contraindications	**n (%)**
Indications	
Neuropathic pain	27 (17.0)
Severe renal impairment	11 (7.0)
Morphine allergy	4 (2.5)
Refractory to other opioids	5 (3.1)
High opioid tolerance	5 (3.1)
Other	6 (4.0)
QTc prolongation/structural heart disease	38 (24.0)
Limited prognosis	12 (6.0)
Contradictions	
Clinically unstable	10 (6.3)
Severe liver impairment	7 (4.4)
Use of other long-acting CNS depressants	5 (3.2)
Drug interactions	5 (3.2)
Limited prognosis (<5 days)	3 (2.0)
Substance use disorder	1 (0.6)
Other	5 (3.2)

CNS: Central nervous system; QTc: Corrected QT interval

3. Accepted methadone recommendations

Out of the 37 pharmacist recommendations, 6 (16.21%) were accepted by the physicians and 2 (8.10%) were implemented by the physicians themselves. Most recommendations provided by pharmacists and physician implemented were provided on Thursday (13; 8.2%).

e. Research question 2

1. Sample stratification

Two groups compared for the inferential analysis were patients provided with pharmacist methadone recommendation (37; 23.4%) and those with no methadone recommendation (121; 76.5%).

2. Methadone recommendations by demographic/clinical characteristics

As per the independent t-test analysis, there was a significant difference in pharmacist methadone recommendations based on the patient's pain intensity score ($p<0.05$). Patients with a high pain intensity score received higher numbers of methadone recommendations compared to patients with lower pain intensity scores (**Table 6**).

Table 6: Differences in continuous variables based on methadone recommendation

Mean (SD)	No methadone recommendation (n=121)	Methadone recommendation (n=37)	T statistic	p-value
Age	81.0 (13.3)	74.6 (14.4)	-2.362	0.091
BMI	24.0 (5.0)	23.0 (5.0)	-1.020	0.310
Pain intensity score	3.0 (1.9)	5.1 (1.5)	6.527	<0.05*
PPS at admission	36.5 (12.0)	39.4 (13.4)	1.241	0.217
PPS after admission	37.0 (12.0)	39.6 (13.0)	1.249	0.214
Days from admission	20.0 (20.0)	28.2 (35.0)	1.362	0.181

* Significant results (>0.05), PPS: Palliative prognosis score; SD: Standard deviation

As per the Chi-square analysis, there was a significant difference between hospice type, terminal indication category, pain type, indication of methadone and whether the pharmacist provides methadone recommendation or not ($p<0.05$). The majority (34; 91.9%) of patients who had an acceptance for methadone recommendation received home hospice service. Cancer patients received higher numbers (25; 67.6%) of methadone recommendations for pain management as compared to other terminal diagnosis. Patients who had both nociceptive and neuropathic type of pain had higher number (16; 43.2%) of methadone recommendations. The most common (15; 40.5%) indication for which methadone recommendation provided was neuropathic pain in patients (**Table 7**).

Table 7: Differences in categorical variables based on methadone recommendation

n (%)	No methadone recommendation (n=121)	Methadone recommendation (n=37)	Chi statistic	p-value
Sex				
Female	72 (46.0)	17 (11.0)	2.150	0.341
Male	47 (30.0)	19 (12.0)		
Hospice type				
Home	87 (55.1)	34 (21.5)	11.548	0.021*
Assisted living	10 (6.3)	0 (0.0)		
Inpatient	0 (0.0)	0 (0.0)		
Nursing home	20 (13.0)	2 (1.3)		
Terminal indication				
Cancer	37 (23.4)	25 (16.0)	16.972	0.018*
Dementia	21 (13.3)	3 (1.9)		
Cardiovascular	36 (23.0)	5 (3.2)		
Respiratory	3 (1.9)	0 (0.0)		
Liver	3 (1.9)	0 (0.0)		
Kidney	3 (1.9)	0 (0.0)		
Neurodegenerative	1 (0.6)	5 (3.2)		
Other	1 (0.6)	6 (3.8)		
Pain type				
Nociceptive	49 (31.0)	13 (8.2)	28.278	0.00*
Neuropathic	1 (0.6)	4 (2.5)		
Both	18 (11.4)	16 (0.1)		
Indication				
Neuropathic	8 (5.1)	15 (9.5)	79.704	0.00*
High opioid	0 (0.0)	2 (1.3)		
Morphine allergy	1 (0.6)	2 (1.3)		
Refractory opioids	2 (1.3)	0 (0.0)		
Several renal impairment	9 (5.7)	0 (0.0)		
Contraindications				
Clinically stable	1 (0.6)	0 (0.0)	15.045	0.18
Drug interactions	1 (0.6)	1 (0.6)		
Limited diagnosis (<5)	3 (1.9)	0 (0.0)		
QTc prolongation	29 (18.4)	4 (2.5)		
Severe liver impairment	6 (3.8)	0 (0.0)		
Other CNS depressant	4 (2.5)	1 (0.6)		

* Significant result (>0.05); CNS: Central nervous system; QTc: Corrected QT interval

f. Characteristics of accepted methadone recommendation patients

In total, eight (21.6%) of 32 pharmacist recommendations were accepted by the physicians. Assessment of the characteristics of all the eight patients in terms of their type of hospice, type and intensity of pain, terminal diagnosis, overall medication history, indication, and contraindication of using methadone is summarized in **Table 8**.

Table 8: Characteristics of patients with accepted methadone recommendations

Study ID	Hospice type	Pain type/ intensity	Terminal diagnosis	Medication history	Indication
52	Home	Both 5	AML	Opioid, APAP, Gabapentin	Neuropathic, other
54	Home	Nociceptive 5	Prostate cancer	Opioid	Other
67	Home	Nociceptive 7	Colon cancer	Opioid, APAP	Other
70	Home	2	Throat cancer	Opioid	
94	Home	3	Lymphoma	Opioid	
100	Home	Both 5	COPD	Opioid	Neuropathic
152	Home	Neuropathic 8	Leukemia	Opioid, Gabapentin, Other	Neuropathic
153	Home	Neuropathic 8	HIV	Opioid	Neuropathic

AML: Adult acute myeloid leukemia; APAP: Acetaminophen; COPD: Chronic obstructive pulmonary diseases; HIV: Human immunodeficiency virus

Patients with study ID 70 and 94 did not receive pharmacist methadone recommendations, but it was implemented by the physician themselves. All of the patients with accepted methadone recommendation were utilizing home hospice. In total, six (75%) out of eight patients had cancer as their terminal diagnosis. Most recommendations for methadone were under the indication of neuropathic pain management (4; 50%); the frequency of pain intensity scores ranging between 5-8 (75%) was high. The allergic conditions of these patients were either not known or were not classified under the categorization used in this study. The listed comorbidities of these patients included cardiovascular disease (6; 75%), respiratory (4; 50%) and kidney (4;

50%) conditions. The majority (6; 75%) of the nutritional statuses of these patients was found to be poor.

II. Phase II of the study

a. Study aims

To identify the frequency and expenditure of medications at various hospice and palliative care settings served by DeltaCareRx. The use of the medications will be evaluated as per therapeutic class and sex of the patient across the pharmacy claims data.

b. Overview

Individual month PBM data from DeltaCareRx sites were employed to analyze the therapeutic class and medication utilization. The trends in the utilization were stratified on patients' sex and the therapeutic class. The cost per patient depending on their sex was calculated for each therapeutic class belonging to the medication categories of interest. Individual drug consumption was evaluated by calculating the total DDD dispensed for the medicines.

c. Sample characteristics

Overall, the dataset consisted of 445 therapeutic class and 3189 medication names. In total 183,450 medications were identified from the categories of interest in the combined dataset of all the six months.

d. Research question 1

1. Frequency in the use and expenditure of each therapeutic class in different months

Descriptive analyses were run using individual month pharmacy claims data to identify the frequency in use of medications, the total cost and monthly mean cost of each therapeutic class along with their standard deviation values (± SD).

i. January

The total number of prescriptions identified in January was 97,260. **Tables 9, 10, and 11** show each therapeutic class's frequency, total costs, and monthly mean average cost with standard deviation associated with each class.

Overall, in the case of pulmonary medications, there was 4.5% of missing cost data. The majority of missing cost data was for sympathomimetic medications (101; 96.2%). **Table 9** shows the frequency, total, and mean monthly cost expenditure for pulmonary medications in January. The average monthly cost was highest for bronchodilator-anticholinergics medications ($171.40) and steroid inhalants ($172.89).

Table 9. Frequency and expenditure of pulmonary medications in January

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	97	$16,770.00	$172.89 ($90.57)	$154.28 ($120.77)
Sympathomimetics	2,169	$79,851.03	$38.61 ($83.43)	$16.87 ($21.93)
Xanthines	26	$2625.06	$58.33 ($50.88)	$31.44 ($78.66)
Bronchodilator-anticholinergic	69	$11,826.80	$171.40 ($196.10)	$23.0 ($411.25)
Leukotriene modulators	41	$277.31	$6.76 ($4.19)	$5.13 ($5.21)

The amount of cost missing data in the case of pain medication was 4.3% and the majority (804; 82.76%) of the cost missing data was found for opioid agonists. **Table 10** demonstrates the frequency in use and cost data for pain medications in January. The medications belonging to the opioid agonist therapeutic class were found to have the highest frequency and highest expenditure.

Table 10. Frequency and expenditure of pain medications in January

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	3,722	$16,499.11	$4.54 ($9.70)	$3.21 ($2.67)
Anesthetics	27	$171.72	$6.90 ($6.40)	$6.58 ($6.02)
Anesthetics topical	337	$8,585.59	$26.17 ($32.64)	$26.13 ($19.16)
Opioid agonists	16,448	$321,495.80	$20.41 ($31.38)	$13.99 ($13.76)
Opioid combinations	1,698	$37,142.27	$22.12 ($21.06)	$16.26 ($15.67)
Opioid partial agonists	3	$314.28	$104.80 ($46.06)	$110.88 (-)
NSAIDS	411	$4,466.11	$11.36 ($55.31)	$11.36 ($4.88)

In the case of anticoagulant medication, there was missing cost data for 3.15% of prescriptions in the database. The majority of cost missing data was found for heparin and heparinoid like agents. **Table 11** demonstrates the frequency in use and cost data for anticoagulant medications in January. The total cost and monthly average cost were higher for direct factor Xa inhibitors than other therapeutic classes in the medication category.

Table 11. Frequency and expenditure of anticoagulant medications in January

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	123	$1,395.41	$11.43 ($32.18)	$3.96 ($3.67)
Direct factor Xa inhibitors	143	$27,424.42	$194.50 ($72.71)	$211.03 ($39.47)
Coumarin anticoagulants	220	$1239.91	$5.74 ($3.55)	$4.94 ($4.41)
Heparin	117	$1135.49	$10.91 ($30.00)	$10.91 ($3.57)

ii. June

The total number of prescriptions identified in June was 128,786. **Tables 12, 13, and 14** show each therapeutic class's frequency, total costs, and monthly mean average cost with standard deviation associated with each class.

Table 12 shows the total expenditure of each class belonging to the pulmonary medication category. The most frequently used therapeutic class was sympathomimetics with higher total expenditure, and the lowest monthly mean cost.

Table 12. Frequency and expenditure of pulmonary medications in June

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	143	$20,944.71	$146.5 ($104.91)	$135.80 ($206.52)
Sympathomimetics	3360	$124,613.04	$37.09 ($68.59)	$18.77 ($19.02)
Xanthines	26	$1,724.29	$45.37 ($42.01)	$26.07 ($39.93)
Bronchodilator-anticholinergic	107	$18,083.71	$169.00 ($198.93)	$20.91 ($412.09)
Leukotriene modulators	41	$701.97	$7.16 ($4.96)	$5.20 ($5.20)
Nasal anticholinergic	6	$227.46	$37.91 ($7.00)	$37.21 ($13.36)

In the case of the pain medication category, there was 0.14% of missing cost data. The opioid agonist therapeutic class had the majority (39; 97.5%) of missing cost data. **Table 13** demonstrates the frequency and total expenditure with the average cost per therapeutic class in the pain medication category.

Table 13. Frequency and expenditure of pain medications in June

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	4,598	$23,111.33	$5.02 ($11.90)	$3.15 ($2.18)
Anesthetics	33	$396.83	$11.20 ($20.38)	$5.13 ($6.49)
Anesthetics topical	579	$15,449.47	$26.68 ($30.84)	$17.38 ($25.0)
Opioid agonists	18,609	$412,862.6	$22.186 ($40.21)	$14.24 ($13.72)
Opioid combinations	2,268	$51,164.52	$22.56 ($83.43)	$16.24 ($17.31)
Opioid partial agonists	7	$2,007.06	$286.81 ($119.73)	$307.01 ($271.66)
NSAIDS	726	$6,818.57	$9.39 ($16.22)	$3.96 ($4.66)

Table 14 demonstrates the frequency and total expenditure with the average cost per therapeutic class in the anticoagulant medication category. The total cost and monthly average cost were higher for Direct factor Xa inhibitors than other therapeutic classes in the medication category.

Table 14. Frequency and expenditure of anticoagulant medications in June

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	249	$2,472.34	$9.93 ($27.21)	$5.15 ($3.60)
Direct factor Xa inhibitors	254	$53,945.07	$212.38 ($65.94)	$219.83 ($16.08)
Coumarin anticoagulants	403	$2,392.38	$5.93 ($3.52)	$4.96 ($3.93)
Heparin	143	$1,406.68	$9.84 ($23.05)	$4.23 ($4.34)

iii. July

In July, there were in total 78,273 prescriptions. Tables 14, 15, and 16 show each therapeutic class's frequency, total costs, and monthly mean average cost with standard deviation associated with each class.

The data for pulmonary medication had missing cost data for 0.63% (n=14) prescriptions. Sympathomimetics and bronchodilator-anticholinergics have the majority of the missing cost data. **Table 15** demonstrates the monthly mean cost for each therapeutic class and the standard of deviation.

Table 15. Frequency and expenditure of pulmonary medications in July

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	68	$10,611.36	$156.00 ($118.71)	$138.0 ($102.4)
Sympathomimetics	1,991	$75,933.73	$38.00 ($77.73)	$18.7 ($20.39)
Xanthines	22	$1,221.96	$56.00 ($53)	$36.71 ($68.33)
Bronchodilator-anticholinergic	78	$11,973.79	$169.00 ($216.54)	$20.91 ($413.0)
Leukotriene modulators	64	$465.34	$7.00 ($5)	$5.20 ($5.81)
Nasal anticholinergic	1	$44.59	-	-

In the case of pain medications, 0.22% of cost data was missing. Medications belonging to the opioid agonist had the majority (31; 88.6%) of missing cost data**. Table 16** shows the frequency, total cost, and average monthly expenditure on every therapeutic class of pain medication category.

Table 16. Frequency and expenditure of pain medications in July

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	2633	$9,894.83	$3.76 ($4.31)	$3.12 ($1.95)
Anesthetics	14	$228.80	$16.34 ($25.11)	$5.13 ($12.48)
Anesthetics topical	413	$12,887.99	$31.20 ($59.28)	$16.80 ($24.10)
Opioid agonists	11,060	$242,094.09	$21.94 ($37.32)	$14.20 ($13.86)
Opioid combinations	1,353	$29,050.80	$21.47 ($19.67)	$16.80 ($16.91)
Opioid partial agonists	2	$448.21	$224.10 ($108.39)	$224.10 (-)
NSAIDS	444	$3,938.72	$8.87 ($14.4)	$4.36 ($5.18)

Table 17 demonstrates the frequency of each therapeutic class of anticoagulant medication in July. The total cost and month mean cost is higher for direct factor Xa inhibitors. Coumarin anticoagulants were found to have the lowest mean average expenditure in the month.

Table 17. Frequency and expenditure of anticoagulant medications in July

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	154	$1,874.12	$12.12 ($32.93)	$5.29 ($4.43)
Direct factor Xa inhibitors	159	$32,307.50	$203.19 ($62.66)	$219.70 ($19.70)
Coumarin anticoagulants	248	$1,428.83	$5.76 ($3.56)	$4.75 ($3.73)
Heparin	88	$1,357.40	$15.43 ($51.6)	$3.48 ($3.29)

iv. September

In total, 134,478 the number of prescriptions were identified in September. **Tables 18, 19, and 20** demonstrate the frequency of each therapeutic class, total costs, and monthly mean average cost with standard deviation associated with each class.

The majority of therapeutic class utilized was found to be sympathomimetics (90.38%) than other therapeutic classes in the pulmonary medication category. The mean average cost lowest for leukotriene modulators ($9). The sympathomimetics had the highest frequency in use (90.30%) and expenditure ($135,346) among all the other therapeutic classes.

Table 18. Frequency and expenditure of pulmonary medications in September

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	104	$20,967	$151.60 ($111.72)	$155.80 ($229.11)
Sympathomimetics	3,648	$135,846	$37.00 ($71.68)	$18.80 ($19.02)
Xanthines	32	$1,425	$45.00 ($48.81)	$21.79 ($35.46)
Bronchodilator-anticholinergic	137	$21,476	$160.00 ($191.44)	$21.34 ($412.12)
Leukotriene modulators	107	$959	$9.00 ($8.35)	$5.57 ($6.48)
Nasal anticholinergic	9	$374	$42.00 ($7.63)	$44.60 ($11.0)

In the case of pain medications, there was missing cost data for 0.11% of medications. The majority (25; 83.3%) of the missing cost data was found for the opioid agonist therapeutic class medications. **Table 19** shows the frequency and mean average cost of each therapeutic class belonging to pain medications. Opioid partial agonists constitute the highest monthly average cost ($164.25) and the lowest frequency (0.2%).

Table 19. Frequency and expenditure of pain medications in September

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	4,655	$17,481.75	$3.75 ($4.08)	$3.10 ($1.85)
Anesthetics	24	$499.20	$20.80 ($32.16)	$5.13 ($18.70)
Anesthetics topical	729	$16,541.09	$22.69 ($26.72)	$15.39 ($20.0)
Opioid agonists	18,936	$411,022.38	$21.70 ($36.62)	$14.24 ($13.70)
Opioid combinations	2,369	$51,420.55	$21.70 ($19.53)	$16.70 ($16.83)
Opioid partial agonists	7	$1,149.78	$164.25 ($115.66)	$147.46 ($42.00)
NSAIDS	847	$8,660.30	$10.22 ($16.78)	$4.43 ($5.95)

Table 20 demonstrates the frequency of therapeutic classes in the anticoagulant medication category and their average monthly cost. Coumarin anticoagulants have the highest frequency (37%) and the lowest monthly average cost ($5.85).

Table 20. Frequency and expenditure of anticoagulant medications in September

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	258	$3,370.06	$13.06 ($32.86)	$4.49 ($3.34)
Direct factor Xa inhibitors	306	$61,918.32	$202.34 ($55.51)	$22.58 ($20.96)
Coumarin anticoagulants	411	$2,404.12	$5.85 ($3.62)	$4.94 ($3.34)
Heparin	143	$2,337.63	$16.34 ($45.75)	$3.82 ($3.60)

v. October

In total, there were 158,830 prescriptions identified in the month of October. **Tables 21, 22, and 23** demonstrate the frequency of each therapeutic class, total costs, and monthly mean average cost with standard deviation associated with each class.

In the case of pulmonary medications, there was 0.9% of missing cost data found for the identified prescriptions. In total, 71.4% of missing cost data was populated by imputing the data from known values in the database for the pulmonary medications.

Table 21 shows the frequency, cost of the expenditure, and average monthly cost of the therapeutic lasses in the pulmonary medication category of October. Sympathomimetics were found to have the highest frequency of use (90.36%) and the highest expenditure ($135,846) with moderately low ($37) monthly mean cost.

Table 21. Frequency and expenditure of pulmonary medications in October

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	197	$24,547.01	$131.26 ($87.50)	$84.70 ($144.50)
Sympathomimetics	4151	$146,610.45	$35.25 ($70.00)	$17.42 ($21.14)
Xanthines	29	$1,658.71	$57.20 ($51.22)	$47.36 ($71.25)
Bronchodilator-anticholinergic	183	$28,578.8	$160.55 ($212.40)	$21.24 ($400.13)
Leukotriene modulators	109	$942.95	$9 ($8.21)	$5.41 ($5.81)
Nasal anticholinergic	14	$487.2	$34.80 ($4.50)	$33.10 (-)

In October's pain medication prescriptions, the cost data were missing for 0.7% of the prescriptions. In total, 20% of missing data was filled by imputing the values from the existing prescription data. **Table 22** shows the frequency, total cost, and monthly average

cost data, which consisted of 0.58% of missing cost data. The highest frequency of use and expenditure was found for the opioid agonist therapeutic class.

Table 22. Frequency of use and expenditure of pain medications in October

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	5,427	$24,170.05	$3.84 ($5.35)	$3.10 ($1.97)
Anesthetics	61	$430.72	$7.55 ($9.40)	$4.68 ($4.49)
Anesthetics topical	864	$19,402.18	$22.45 ($27.88)	$15.52 ($16.13)
Opioid agonists	22,600	$475,431.75	$21.20 ($35.72)	$13.45 ($14.36)
Opioid combinations	2596	$58,755.08	$22.63 ($21.51)	$17.71 ($17.83)
Opioid partial agonists	4	$1,481.06	$370.26 ($176.98)	$325.04 ($323.81)
NSAIDS	965	$9,481.32	$9.82 ($16.00)	$5.03 ($6.20)

Table 23 demonstrates the frequency and cost data for the anticoagulant medications in the month of October. Direct factor Xa inhibitors were found to have the highest expenditure and higher monthly mean cost ($202.34) compared to other therapeutic classes in the medication category.

Table 23. Frequency and expenditure of anticoagulant medications in October

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	289	$4,267.05	$14.81 ($38.03)	$5.29 ($3.68)
Direct factor Xa inhibitors	330	$69,484.23	$210.55 ($58.49)	$220.51 ($19.83)
Coumarin anticoagulants	472	$2,668.22	$5.74 ($3.57)	$5.04 ($4.27)
Heparin	193	$5,521.28	$28.90 ($75.04)	$3.48 ($4.44)

vi. November

In total, there were 134,840 prescriptions identified in the month of November. **Tables 24, 25, and 26** demonstrate the frequency of each therapeutic class, total costs, and monthly mean average cost with standard deviation associated with each medication category.

In the pulmonary medication category, 12.3% of cost data was found to be missing for the prescriptions. In total (425; 25.4%) of missing cost data was filled with the help of imputing technique. **Table 24** consists of frequency, total cost, and mean average cost from the pulmonary medication data, which has (337; 9.18%) of missing cost data. The sympathomimetics were found to have the highest utilization and expenditure with moderate month mean cost. The overall expenditure of pulmonary medications in November was the highest ($200,430.90) compared to other months' data.

Table 24. Frequency and expenditure of pulmonary medications in November

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Steroid inhalants	200	$27,697.12	$152.18 ($114.70)	$137.50 ($52.85)
Sympathomimetics	4,943	$152,986.75	$32.90 ($55.61)	$19.25 ($15.22)
Xanthines	38	$1,502.88	$44.20 ($43.87)	$21.79 ($48.0)
Bronchodilator-anticholinergic	147	$17,395.88	$168.89 ($196.66)	$21.29 ($412.39)
Leukotriene modulators	130	$766.46	$7.36 ($4.93)	$6.0 ($5.01)
Nasal anticholinergic	2	$81.8	$41 ($6.30)	-

In the pain medication category, (7311; 34%) of cost data was found to be missing for the prescriptions. From the total missing data (6045; 23.24%) of cost data was filled by imputing the values. **Table 25** shows the values from the database, which consisted of 28% of missing cost data. Opioid agonists had the highest utilization and expenditure among all the therapeutic classes. The analgesics medication had the lowest ($3.90) mean average cost value.

Table 25. Frequency and expenditure of pain medications in November

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Analgesics	6,613	$24,079.25	$3.90 ($4.31)	$3.32 ($1.62)
Anesthetics	26	$301.47	$17.73 ($29.64)	$5.87 ($9.37)
Anesthetics topical	1,032	$16,217.97	$23.04 ($24.70)	$16.06 ($17.97)
Opioid agonists	26,223	$478,817.92	$22.74 ($35.89)	$15.22 ($12.78)
Opioid combinations	3,286	$50,281.78	$22.16 ($19.98)	$16.82 ($16.59)
Opioid partial agonists	8	$2,231.58	$278.94 ($166.55)	$231.0 ($141.11)
NSAIDS	1,178	$7,665.50	$9.12 ($16.74)	$4.30 ($5.0)

In the case of the anticoagulant medication category, the prescription had 60% of missing data for cost. The missing data filled by imputing was about 26%. A high percentage (50%) of missing quantity data caused higher missing cost data and a low number of imputed values in the database. **Table 26** demonstrates the values from the database, which consisted of 47% of missing cost data. The majority (38.03%) of missing cost data was for coumarin anticoagulant's prescriptions. Direct factor Xa inhibitors were found to have the highest utilization, expenditure, and mean average cost value.

Table 26. Frequency and expenditure of anticoagulant medications in November

Therapeutic class	Frequency	Total cost	Monthly mean cost (SD)	Monthly median cost (IQR)
Platelet aggregation inhibitors	269	$4123.84	$15.38 ($37.03)	$5.29 ($4.31)
Direct factor Xa inhibitors	461	$67,795.13	$214.54 ($69.93)	$220.32 ($19.86)
Coumarin anticoagulants	421	$2394.0	$6.0 ($3.36)	$5.05 ($3.50)
Heparin	128	$10,968.53	$86.36 ($169.41)	$4.85 ($24.90)

e. Overall costs per therapeutic class in the combined dataset of all the months

i. Pain medication category

In total 154,576 pain medication claims were identified from the combined dataset. The data consisted of missing cost data (8574, 5.54%). **Table 27** shows the descriptive statistics of pain medication category in the combined data set from all the months.

Table 27. Overall cost descriptive statistics for pain medication category

Therapeutic class	Mean (SD)	Median (IQR)
Analgesics	$4.28 ($8.04)	$3.16 ($2.00)
Anesthetics	$11.77 ($20.37)	$5.13 ($6.60)
NSAIDS	$9.71 ($24.54)	$4.34 ($4.94)
Opioid combinations	$22.16 ($20.75)	$16.48 ($16.63)
Opioids agonists	$21.75 ($36.33)	$14.24 ($13.76)
Partial agonists	$246.21 ($230.97)	$230.97 ($159.55)
Topical anesthetics	$24.62 ($19.50)	$16.53 ($19.50)

ii. Pulmonary medication category

In total, 22,523 pulmonary prescription data were found in the combined dataset of all the months. The data consisted of missing cost data (484, 2.15%). **Table 28** shows the descriptive statistics of pain medication category in the combined data set from all the months.

Table 28. Overall cost descriptive statistics for pulmonary medication category

Therapeutic class	Mean (SD)	Median (IQR)
Bronchodilator – anticholinergic	$165.16 ($201.87)	$21.28 ($412.40)
Leukotriene modulators	$7.89 ($6.51)	$5.36 ($5.81)
Nasal anticholinergic	$37.53 ($6.61)	$33.31 ($11.79)
Steroid inhalants	$140.67 ($106.94)	$137.50 ($122.56)
Sympathomimetics	$36.04 ($69.44)	$18.50 ($19.53)
Xanthines	$51.00 ($47.93)	$26.07 ($68.00)

iii. Anticoagulant medication category

In total, 6,351 pulmonary prescription data were found in the combined dataset of all the months. The data consisted of missing cost data (570, 9%). **Table 29** shows the descriptive statistics of pain medication category in the combined data set from all the months.

Table 29. Overall cost descriptive statistics for anticoagulant medication category

Therapeutic class	Mean (SD)	Median (IQR)
Coumarin anticoagulants	$6.00 ($3.52)	$4.94 ($3.84)
Direct factor Xa	$207.75 ($63.80)	$219.85 ($19.64)
Heparin	$28.55 ($3.74)	$3.74 ($4.19)
Platelet aggregation inhibitors	$13.07 ($5.29)	$5.30 ($8.84)

f. Research question 2

The dataset of each month was stratified as per the patient's sex. The cost for each subset was calculated. Total data of dispensed medications of interest were found for 88,601 male and 124,389 female patients

1. Trends in utilization as per patients' sex

Table 30 demonstrates the stratification of frequency data as per the patient's sex for all the anticoagulant medications. The patient's sex data was missing for certain prescriptions in the month of January (1.7%), June (50%), and for the month of November due to 47% of missing cost data the expenditure was found to be lower compared to the frequency of the use of certain medications. In the majority of months, the frequency of anticoagulants used in female patients was found to be higher. The therapeutic class most frequently used in all the months in male and female patients was coumarin anticoagulants. In terms of expenditure, direct factor Xa inhibitors constituted the highest expenditure in all the months for both males and females.

Table 30: Trends in anticoagulant medication utilization as per patients' sex

Month	Frequency in male patients	Cost	Frequency in female patients	Cost
January	271	$11,203.52	319	$19,968.23
June	222	$12,773.13	304	$19,230.51
July	266	$16,685.28	383	$20,282.57
September	466	$28,061.88	652	$41,968.25
October	583	$36,278.42	727	$47,321.07
November	666	$31,412.59	1,003	$53,868.90

Table 31 shows similar stratification data for patients using pain medications. The patient's sex data was missing for certain prescriptions in the month of January (0.5%) and June (47.4%) and 25% of missing cost data for the prescriptions in November. The values for pain medication categories were highest for both females and males than other medication

categories. Female patients had a higher pain medication utilization. Opioid agonist was found to be the most commonly used class in both males and females. In June and July, opioid combinations used in females were found to form a significant part of the expenditure of the therapeutic class ($113,121.07 and $126,663.8). In November, female patients were found to be administered the highest in the number of pain medications such as non-steroidal anti-inflammatory drugs (805; 3%), opioid combinations (2,235; 0.9%), and opioid agonists (17,745; 68%).

Table 31: Trends in pain medication utilization as per patients' sex

Month	Frequency in male patients	Cost	Frequency in female patients	Cost
January	9,362	$161,651.25	13,171	$223,667.19
June	5,715	$113,121.07	8,355	$154,670.72
July	6,425	$126,663.8	9,469	$171,739.3
September	11,252	$215,511.2	16,315	$291,263.9
October	13,754	$258,542.05	18,865	$293,689.88
November	15,344	$239,861.60	22,117	$310,604.4

Table 32 demonstrates trends in all the therapeutic classes of pulmonary medication utilization as per the patient's sex. The patient's sex data was missing for certain prescriptions in January (1.5%) and June (47.2%). The missing cost data (9.18%) in the month of November shows the cost values lower compared to the frequency in use of medications. Sympathomimetics were highly used in both males and females; it constituted the high expenditure in all the months.

Table 32: Trends in pulmonary medication utilization as per patients' sex

Month	Frequency in male patients	Cost	Frequency in female patients	Cost
January	1,050	$52,288.81	1,322	$55,591.52
June	824	$33,681.99	1,062	$43,822.29
July	940	$41,184.77	1,284	$59,066.00
September	1,755	$79,736.37	2,213	$100,913.4
October	1,954	$88,792.66	2,725	$114,032.46
November	2,388	$87,879.98	3,072	$112,550.92

2. **The difference in mean cost per patients across individual months and all the months**

Table 33 and **Table 34** demonstrate the differences in mean cost per male and female patients across three medical categories. The mean cost per patient values for June differentiate from the other months due to significant missing gender data that was 50% of the total anticoagulant medications, 47.4% of the total pain medications and 47% of the total pulmonary medications. The mean of the cost per patients were found to be higher for June, September, and November because of comparatively higher proportions of opioid partial agonist prescriptions in the particular month's pharmacy claims data.

Table 33. Differences in per male patient mean cost across three medical categories

Month	Mean cost per male patients (anticoagulants)	+/- SD	Mean cost per male patients (pain)	+/-SD	Mean cost per male patients (pulmonary)	+/-SD
January	$48.16	$86.54	$15.12	$8.60	$66.95	$73.05
June	$58.05	$104.54	$51.75	$112.45	$58.15	$78.50
July	$61.00	$98.47	$14.71	$12.73	$66.82	$70.49
September	$58.70	$91.12	$40.35	$60.57	$60.72	$65.65
October	$63.44	$86.021	$14.63	$8.28	$74.84	$66.66
November	$50.27	$64.92	$39.00	$81.56	$61.48	$64.50

SD: standard deviation

Table 34: Differences in per female patient mean cost across three medical categories

Month	Mean cost per female patients (anticoagulants)	+/- SD	Mean cost per female patients (pain)	+/- SD	Mean cost per female patients (pulmonary)	+/- SD
January	$60.80	$93.66	$25.39	$27.83	$68.28	$82.54
June	$60.50	$103.33	$48.54	$78.06	$53.94	$66.62
July	$57.40	$94.65	$19.55	$16.10	$72.02	$79.92
September	$60.00	$98.76	$30.94	$44.31	$74.80	$67.15
October	$63.60	$83.40	$11.00	$9.21	$66.31	$53.69
November	$57.70	$66.50	$37.27	$91.24	$71.31	$74.75

SD: standard deviation

g. Research question 3

The utilization of the medications was calculated using the quantity and strength data of the prescriptions available in the database. The quantity data for the prescriptions was

missing for the months of January, June and July. Therefore, DDD values was calculated for prescriptions in the months of September, October and November.

Consumption level of anticoagulants varied during the months of September, October, and November (**Table 35**). Heparin was highly consumed in all the three months (638 DDDs dispensed, 627 DDDs and 22,095 DDDs). Warfarin consumption level was found to be stable in the months of October (43 DDDs) and November (40 DDDs). The overall pattern in use of anticoagulants as per the PBM data was not found to be consistent.

Table 35. Total anticoagulant medication DDDs dispensed

Generic long names	September	October	November
apixaban	85.03	40.00	41.80
heparin	637.73	627.93	22,095.17
warfarin	7.00	43.00	39.75
cilostazol	4.75	1.45	1.50
ticagrelor	-	1.50	2.10
rivaroxaban	28.25	15.45	16.88
prasugrel	0.50	-	0.50
clopidogrel	128.13	68.00	76.96
enoxaparin	147.00	248.22	160.00

In the case of pain medications, consumption level was seen uniform for acetaminophen and morphine (**Table 36**). Hydromorphone utilization uniformly increased from 517 DDDs in September to 1209 DDDs in November. Overall consumption of the following medications, ibuprofen (193 DDDs), methadone (741 DDDs), Oxycodone (628 DDDs) and tramadol (338 DDDs), was found to higher in September. The consumption of fentanyl was lowest in October (5 DDDs) and November (0.005 DDD) and highest in September (6346 DDDs).

Table 36. Total pain medication DDDs dispensed

Generic long names	September	October	November
APAP	626.92	489.44	520.70
diclofenac	10.10	0.206	0.173
ibuprofen	193.00	98.40	91.30
indomethacin	3.01	1.12	23.6
ketorolac	1.80	0.42	-
meloxicam	104.15	61.52	51.36
celecoxib	36.92	15.22	17.80
piroxicam	-	-	0.5
oxaprozine	13.33	-	0.66
etodolac	3.00	-	1.00
hydromorphone	517.22	1052.4	1209.50
methadone	741.70	368.45	337.60
morphine	1934.32	1095.10	1111.72
oxycodone	628.25	355.87	362.23
tramadol	337.64	136.36	178.11
buprenorphine	1.67	0.043	0.003
codeine	6.31	1.06	0.75
fentanyl	6345.84	5.46	0.01

Table 37 shows the comparable values of consumption for the pulmonary medications across the three months. Pulmonary medication like albuterol, fluticasone, ipratropium, theophylline was most commonly consumed in all the three months.

Table 37. Total pulmonary medication DDDs dispensed

Generic long names	September	October	November
albuterol	27,534.50	13,822.40	14,793.50
budesonide	71.00	34.35	53.00
beclomethasone	-	0.10	-
fluticasone	5.40	4.17	2.00
ipratropium	575.72	217.97	242.56
tiotropium	51.00	0.03	18.00
theophylline	17.13	7.31	7.10
phenylephrine	8.42	4.21	0.30
pseudoephedrine	966.70	564.51	866.60

CHAPTER 5: DISCUSSION

I. Key findings

The current study described the prevalence of pharmacists' methadone recommendation and medication utilization in hospice and palliative care settings. Phase I of the study prospectively evaluated the rate of pharmacists' methadone recommendations and their acceptance at DeltaCareRx's facilities. The second phase of the study retrospectively assessed the frequency and expenditure of utilizing pain, pulmonary, and anticoagulants medication at various DeltaCareRx client sites. The primary focus of the research study was identifying potential ways for cost optimization at various client sites of DeltaCareRx.

The results of the systematic literature review conducted in this study support the recommendation made by ASHP of involving clinical pharmacist in hospice and palliative care multidisciplinary team. Although the objective of the study was assessing medication utilization including methadone at DeltaCareRx's client sites the current literature review answers a slightly different research question. A pilot systematic review was conducted in the initial stages of the study to lay the foundation of methadone use in hospice and palliative care settings and its cost-effectiveness properties. The literature review consisted of key terms such as methadone, hospice care setting, cost, and clinical benefits. However, the preliminary search strategy failed to generate a higher number of evidence articles for the hypothesis. The archived articles demonstrated the benefits of using methadone in all types of pain, cancer-related pain, and its cost-effectiveness as compared to other opioids.[45,77,78]

The increasing expenditure and resources used in hospice and palliative care requires cost savings to be generated at the hospice provider sites.[79] Few of the suggested ways include the use of PBM services to secure lower for the prescription drugs, leveraging pharmacist role in the multidisciplinary team, ensure adherence to the formulary, and serving patients with cost-effective medications to achieve desirable outcomes.[80] Cost analysis in end-of-life care is challenging due to difficulties quantifying the quality of life concept in patients treated for their terminal illness. The need for cost saving in this setting requires

implications of various ways for cost containment.[21] Therefore, the study explores the prevalence of cost-effective methadone medication and the overall frequency, expenditure, and consumption of medications at the hospice and palliative care DeltaCareRx sites. The methadone use results provide evidence of popularity in using the cost and clinically effective medication for pain management.[81] The results of evaluating frequency and expenditure of the most population medication categories pain, pulmonary, and anticoagulants provide a head start to develop cost containment strategies at DeltaCareRx client sites.

The results of phase one included the prevalence of methadone recommendation and its acceptance in patients admitted at DeltaCareRx's hospice and palliative care sites. The pharmacist data collection tool #1 identified patients' demographic and clinical characteristics. The majority of patients opted for home hospice type of care and observed experiencing both nociceptive and neuropathic pain. The overall prevalence and acceptance of methadone recommendations were too low.

ASHP endorsed methadone for its use in pain relief as an effective medication use in hospice and palliative care. [82] Methadone use for pain relief suggests constant monitoring of patients and titration of doses frequently.[39] Current study provides potential reasons for the low use of methadone in hospice and palliative care settings. The literature identifies two conditions for low methadone use in patients with pain, which are QTc prolongation and respiratory disorders.[83] In the current study, QTc prolongation was one of the conditions found to be common among patients. In alignment with the literature, this can be one of the potential reasons for the low prevalence and acceptance of methadone recommendation.

The low acceptance rates of pharmacist's recommendations also raise a concern regarding awareness of methadone use for pain management. Hawely *et al*. explore the barriers to continuing methadone prescription for pain management. Despite patients' willingness to receive methadone, there were barriers to receiving the treatment. The low popularity and knowledge about the use of methadone among healthcare professionals contributed to its

low accessibility.[84] According to the literature, methadone is a potential treatment for neuropathic pain because it is an N-methyl-D-aspartate (NMD) receptor antagonist and prevents monoamine reuptake.[85] Results in the current study supports the effectiveness of methadone in this type of pain. The accepted methadone recommendation was most commonly accepted in patients with neuropathic pain (4 out of 8; 50%).

The Medicare billing policy changes encourage hospice cost-sharing for medication utilization. Various measures are taken to promote the optimization of cost containment and quality improvement for hospice providers. One such way is episode-based payment models, which "*gives health care providers a spending target for most types of care provided during a clinical episode (e.g., six months of chemotherapy, an inpatient admission or outpatient procedure plus most other care provided in the subsequent 90 days). If total spending is less than the target, Medicare pays providers a bonus; if total spending is more than the target, Medicare recoups money from providers*."[86]

In order to start developing cost-saving strategies for DeltaCareRx's hospice providers, it was essential to study the overall utilization of the most common medication categories in hospice and palliative care settings. PBM claims data obtained from DeltaCareRx was analyzed for this purpose. Overall, the frequency of pain medication use was comparatively higher than that of pulmonary and anticoagulant medication categories. Opioid agonists were most frequently used across the months. According to literature, opioids are prevalent in use at hospice and palliative care sites due to pain being one of the important symptoms experienced by these patients.[87]

The key findings of the analysis demonstrate the frequency in the use of therapeutic classes, their total and average monthly expenditure. It displays the overall expenditure between various classes of individual medication categories. The findings can assist in designing and executing a cost-saving strategy for each category. The known clinically effective but cost-effective medications can be used more than the expensive ones from particular categories. For example, the total DDDs of morphine medication dispensed is uniformly higher in all the months. In terms of consumption of cost-saving medications like

methadone was found to be as much as other opioid medications. Overall, it displays a comparable use of this medication among the pain medications at different hospice and palliative care sites of DeltaCareRx.

In November, the frequency in use of pulmonary medications was the highest (5,460), and due to missing cost data (9.18%), the total expenditure ($200,430.81) did not align with the frequency. The average costs for pulmonary medications per male patients and female patients across all the months was found to be $64.82 and $67.77. Sympathomimetics (like albuterol, ipratropium, ipratropium bromide, arformoterol) was the most commonly used therapeutic class. The expenditure of sympathomimetics was also found higher in all the months. The average cost of the overall class in all the months was between the range of ($31-$38). This implies that the therapeutic class used in this class does not increase the expenditure of the overall medication category.

Coumarin anticoagulants (warfarin sodium), had a uniform frequency in use across all the months (January – 32%, June – 32.41%, July – 38.21%, September – 38%, October – 36.80%, November – 37.44%). The average costs for anticoagulant medications per male patients and female patients across all the months was found to be $56.60 and $60.00. Among all the therapeutic classes in the anticoagulant medication category, direct factor Xa medications (like rivaroxaban and apixaban) were found to have the highest monthly mean in all the months. Therefore, the formulary at DeltaCareRx can include cost-effective direct factor Xa medications to increase cost savings at the client sites.

The frequency in use of opioid agonists (like morphine, fentanyl, hydromorphone, oxycodone, tramadol, methadone) in all the six months was high (January – 72.61%, June – 69.40%, July – 69.70%, September – 70.20%, October – 71.16%, November – 68.35%). The overall frequency of pain medication was higher, but the per male and female patient cost was not found to be that higher ($29.30 and $28.77). The higher prevalence of pain symptoms among hospice and palliative care patients increases the overall use of these drugs, increasing the total expenditure. The use of opioid partial agonists (like buprenorphine) varied throughout the months. The higher cost of the medication in this

therapeutic class skewed the overall monthly mean cost for September, October, and November. In terms of the pain medication category, any cost-effective medication used in any therapeutic class will help in overall cost optimization at DeltaCareRx sites. The results from the phase I of the study can be useful in road mapping an increase in the use of methadone at the client sites to increase cost savings.

The prescription claims data obtained from DeltaCareRx identifies the cost savings associated with methadone use at client sites. Methadone belongs to the opioid agonist therapeutic class. In the combined data set of all the months, the overall frequency and expenditure of methadone was found to be 10,993 and $110,376.49. The overall frequency and expenditure of all other opioid agonists was found to be 48,305 and $135,79,26.494. Therefore, the average expenditure of using methadone ($10) was lower compared to all other opioid agonists ($28).

The key finding of the analysis evaluating medication utilization as per sex of the patient demonstrated higher use of pain medication among female patients. In alignment with the evidence available in the literature that women patients have the higher chances of receiving pain medications. There are various explanation for this bais in use of pain management medications such as high incidence of osteoporosis among women, biological factors, higher adverse events of analgesic use in men compared to women and at time phycians's gender also influences their clinical judgemnet of medication prescription to their male or female patients. [88,89]

Evaluation of medication consumption was evaluated using DDD values of individual medications in different months. The advantage of using the DDD methodology is that the utilization of the medications can be compared across different months in a standardized manner. The DDD values vary throughout due to differences in the consumption of medications with specific strength and quantity. This can be explained with an example such as warfarin consumption in September (7 DDD), October (42 DDD), and November (39.95 DDD). The consumption of warfarin tablets with a 7.5 mg strength was higher in October and November than in September.

Heparin and heparinoid-like agents such as enoxaparin were the most commonly utilized anticoagulant medications in all the three months. The most commonly utilized direct factor Xa inhibitor was apixaban and rivaroxaban. The utilization of opioid agonists was found to be consistent in all three months, which was followed by APAP. The utilization of different NSAIDs varied across the three months. Albuterol had higher consumption values in all three months.

The major disadvantage of using DDD methodology is the difference between the prescribed daily dose and WHO recommended DDD. Another limitation is that the DDD values do not account for the potency of the drugs but depends on the frequency in use of the dose of each drug.[90] Also, the database used for this study consisted of missing quantity values for the prescriptions. This influences the DDD values acquired for a particular medication. Additionally, the DDD values for combinations products other than products listed in Appendix 4 was not available on the WHO DDD website. The database consisted majorly of these combination products whose consumption cannot be studied due to the unavailability of DDD values.

II. Limitations and future considerations

The study consisted of some limitations that may have impacted the results and are important to consider for a clear interpretation of the study results.

a. Clinical outcomes of methadone use

The study evaluates the prevalence and acceptance of methadone recommendations. As a part of future research avenues the accepted methadone recommendations can be followed up for clinical outcomes. The clinical benefit of methadone use can be studied by following the accepted patients for methadone use. A clinical trial study in patients with chronic and opioid dependence when treated with methadone demonstrated improvement in pain compared to buprenorphine.[91] Methadone has clinical advantages of relieving chronic pain, longer half-life, safety in use despite renal and liver disease, and no active metabolites. [39]

These treatment benefits can be identified by following the patients for their improvement in pain management.

b. Generalizability

The data for phase one was collected from selective sites of DeltaCareRx. The geographical location of the selected sites was not available to the researchers. The collected data was not from all the sites of DeltaCareRx. This bias the study results. The methadone recommendation might be low only at DeltaCareRx sites compared to other hospice and palliative care settings. A comparative study between DeltaCareRx sites and non DeltaCareRx hospice providers can help understand these differences in methadone use.

c. Limitation of using PBM claims database

The PBM claims database did not have any lab values such as patient's pain scores, FEV1 values, partial thromboplastin time (PTT), etc. of the patients. Therefore, the clinical benefit of using the medications was not quantified. The differences in higher and lower consumption levels of various medications could have been aligned with the patients' disease condition's incidence.

d. Impact of missing data

The inclusion of data from all the months of 2019 will help evaluate the trends in the utilization of the medications over a year. The results based on the individual month data are standalone and cannot be extrapolated to the use of medications in the whole year. Also, geographical differences in the frequency of medication use and its costs can be valuable to study. The facility-based evaluation will allow exploring differences in the utilization of medications as per their geography.

III. Study implications and conclusion

Overall, the study provides evidence on the use of the pharmacist role and medication utilization in hospice and palliative care settings. As per ASHP inclusion of pharmacists does have a positive impact on the multidisciplinary hospice team. In this study, it was seen

that the pharmacists' recommendation helped in increasing the probability of the use of cost-effective treatments like methadone. The use of methadone in hospice and palliative care setting is still a topic of discussion. The results of this study support the evidence of its low popularity of use due to various reasons. The study provides a starting point in understating the prevalence of methadone use in a real-world setting. The findings from this research have implicated on importance of methadone use at DeltaCareRx sites and how can the staff be trained on its use. The frequency and monthly average cost results will help to develop a roadmap of increasing the use of cost-effective medications. The formulary provided to the hospice sites by DeltaCareRx may include medications that were most frequently used and less costly.

REFERENCES

1. Medicare-hospice-benefits. In. CMS: Centers for Medicare and Mediciad services; 2019.
2. WHO. WHO defination of palliative care. https://www.who.int/cancer/palliative/definition/en/. Accessed November 4, 2019.
3. Palliative Care vs. Hospice Care. Centers for Medicare and Medicaid services. https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Downloads/infograph-PalliativeCare-[June-2015].pdf. Published 2015. Accessed November 4, 2019.
4. Facts and figures hospice care in America. https://legacy.nhpco.org/sites/default/files/public/Statistics_Research/2017_Facts_Figures.pdf. Published 2017. Accessed November 28, 2019.
5. NHPCO facts and figures National Hospice and Palliative Care Organization https://www.nhpco.org/wp-content/uploads/2019/07/2018_NHPCO_Facts_Figures.pdf. Published 2018. Accessed November 28, 2019.
6. America's Care of Serious Illness. Center to Advance Palliative Care A STATE-BY-STATE REPORT CARD ON ACCESS TO PALLIATIVE CARE IN OUR NATION'S HOSPITALS Web site. Published 2019. Accessed November 18, 2019.
7. Dumanovsky T, Augustin R, Rogers M, Lettang K, Meier DE, Morrison RS. The Growth of Palliative Care in U.S. Hospitals: A Status Report. *J Palliat Med.* 2016;19(1):8-15.
8. Care CtAPCaNP. America's care of serious illness https://reportcard.capc.org/. Accessed 05/08, 2020.
9. Quality of Life Matters: End of life care news and clinical findings for physicians. NewsLine Web site. https://www.wregional.com/Uploads/Public/Documents/Hospice/Hospice_QOLM_18-3_newsletter.pdf. Accessed December 23, 2019.
10. Jennifer S. Temel MD, Joseph A. Greer, Ph.D., Alona Muzikansky, M.A.,, Emily R. Gallagher RN, Sonal Admane, M.B., B.S., M.P.H.,, Vicki A. Jackson MD, M.P.H., Constance M. Dahlin, A.P.N.,, Craig D. Blinderman MD, Juliet Jacobsen, M.D., William F. Pirl, M. Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer. *The New England journal of Medicine.* 2010.
11. Bakitas MA, Tosteson TD, Li Z, et al. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol.* 2015;33(13):1438-1445.
12. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *The Lancet.* 2014;383(9930):1721-1730.
13. Dalal S, Bruera E. End-of-Life Care Matters: Palliative Cancer Care Results in Better Care and Lower Costs. *The Oncologist.* 2017;22(4):361-368.
14. *Medciare Payment Policy: reprot to Congress.* March 2019.
15. Hospice Costs & End-of-Life Options. https://www.debt.org/medical/hospice-costs/. Accessed December 10, 2019.

16. Commision MPA. Report to Congress: Medicare Payment Policy. CMS http://www.medpac.gov/docs/default-source/reports/mar19_medpac_entirereport_sec.pdf. Published 2019. Accessed December 22, 2019.
17. Medicare Hospice Payment Reform: A Review of the Literature. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/Hospice/Downloads/HPR-Lit-Review-Update-Report-.pdf. Updated May 4, 2015. Accessed December 22, 2019.
18. Services CfMaM. MedicareHospicePaymentReformLiteratureReview2013. Abt Associates Inc. . Published 2013. Accessed 05/27, 2020.
19. Field MJ, Cassel CK. *Approaching death. [electronic resource] : improving care at the end of life.* National Academy Press; 1997.
20. Duncan I, Ahmed T, Dove H, Maxwell TL. Medicare Cost at End of Life. *Am J Hosp Palliat Care.* 2019;36(8):705-710.
21. Ozanne KBaE. Importance of Costs and Cost Effectiveness of Palliative Care 2017;13(5).
22. Kelley AS, Deb P, Du Q, Aldridge Carlson MD, Morrison RS. Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay. *Health Aff (Millwood).* 2013;32(3):552-561.
23. Cynthia G. Tudor PD, Director Medicare Drug Benefit and C & D Data Group, Laurence Wilson, Director Chronic Care Policy Group, Mark Majestic, Director Medicare Program Integrity Group All Part D Plan Sponsors and Medicare Hospice Providers. In: Centers for Medicare and Medicaid Services; 2013.
24. Role of Pharmacist in Palliative care. *Oncology Nursing Society Country of Publication: United States.* 2015 Vol. 30 (2),:pp. 33.
25. Revisions to Chapter 2, "The Certification Process," Sections 2080 – 2089. In: & DoH, (DHHS) HS, & CfM, (CMS) MS, eds. Pub. 100-07 State Operations Provider Certification: CMS; October 1, 2010.
26. *ASHP Statement on the Pharmacist's Role.* 2002.
27. Herndon CM, Nee D, Atayee RS, et al. Ashp guidelines on the pharmacist's role in palliative and hospice care. *American Journal of Health-System Pharmacy.* 2016;73(17):1351-1367.
28. Jimmie P. Leleszi D, Jeanne G. Lewandowski, MD Pain Management in End-of-Life Care. *The Journal of the American Osteopathic Association.* March 2005;Vol 105(No 3).
29. Clinical Practice Guidelines for Quality Palliative Care, 4th edition. Published 2018. Accessed January 17, 2020.
30. National Hospice and Palliative Care Organization https://www.nhpco.org/. Accessed December 1, 2020.
31. Bennett MI, Kaasa S, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. *Pain.* 2019;160(1):38-44.
32. (WHO) WHo. ICD-11. https://www.who.int/classifications/icd/en/. Accessed 05/08, 2020.
33. WHO. Palliative Care: symptom management and end-of-life care. Integrated Management of Adolescent and Adult Illness Web site. Published 2004. Accessed January 17, 2020.

34. Klein C, Lang U, Bukki J, Sittl R, Ostgathe C. Pain Management and Symptom-Oriented Drug Therapy in Palliative Care. *Breast Care (Basel).* 2011;6(1):27-34.
35. Blondell MA, MD; and Wisniewski, PharmD. Pharmacologic Therapy for Acute Pain. Published 2013. Accessed January 17, 2020.
36. Groninger MV, MD. Pharmacologic Management of Pain at the End of life. Published 2014. Updated July 1, 2014. Accessed January 17, 2020.
37. Care IAfHaP. World Health Organization Essential Medication list Palliative care. https://www.who.int/selection_medicines/committees/expert/19/applications/PalliativeCare_8_A_R.pdf. Published 2013. Accessed January 20, 2020.
38. Medscape. Methadone, Pain Management, and Palliative Care. https://www.medscape.org/viewarticle/550895. Accessed.
39. John F. Manfredonia D. Prescribing Methadone for Pain Management in End-of-Life Care. 2005;105(3).
40. John F. Manfredonia D. Using Methadone to Control Pain in Patients During Final Stages of Life. *The Journal of the American Osteopathic Association.* 2007;Vol 107(No 6).
41. Douglas J. Weschules P, * Jill A. McMath, PharmD,* Rollin Gallagher, MD, MPH,*† Calvin J. Alt, RPh,* and Calvin H. Knowlton, RPh, MDiv, PhD* Methadone and the Hospice Patient: Prescribing Trends in the Home-Care Setting. 2003;4.
42. Watson CP. Methadone for neuropathic pain: a new use for an old drug? *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques.* 2005;32(3):271-272.
43. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. *Postgrad Med J.* 2004;80(949):654-659.
44. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain.* 2014;15(4):321-337.
45. McPherson ML, Walker KA, Davis MP, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. *J Pain Symptom Manage.* 2019;57(3):635-645 e634.
46. George PP, Molina JA, Cheah J, Chan SC, Lim BP. The evolving role of the community pharmacist in chronic disease management - a literature review. *Ann Acad Med Singapore.* 2010;39(11):861-867.
47. Pharmacist-managed pain clinic at a Veterans Affairs medical center. *Am J Health-Syst Pharm.* 2004;Vol 61.
48. Hadi MA, Alldred DP, Briggs M, Munyombwe T, Closs SJ. Effectiveness of pharmacist-led medication review in chronic pain management: systematic review and meta-analysis. *Clin J Pain.* 2014;30(11):1006-1014.
49. DeltaCareRx. https://www.deltacarerx.com/. Accessed February 2, 2020.
50. Blouin RA, Adams ML. The Role of the Pharmacist in Health Care: Expanding and Evolving. *N C Med J.* 2017;78(3):165-167.

51. Richter C. Implementation of a Clinical Pharmacist Service in the Hospice Setting: Financial and Clinical Impacts. *J Pain Palliat Care Pharmacother.* 2019:1-4.
52. Valgus J, Jarr S, Schwartz R, Rice M, Bernard SA. Pharmacist-led, interdisciplinary model for delivery of supportive care in the ambulatory cancer clinic setting. *Journal of Oncology Practice.* 2010;6(6):e1-e4.
53. Bennett MI, Bagnall AM, Raine G, et al. Educational interventions by pharmacists to patients with chronic pain: systematic review and meta-analysis. *Clin J Pain.* 2011;27(7):623-630.
54. Selçuk AA. A Guide for Systematic Reviews: PRISMA. *Turk Arch Otorhinolaryngol.* 2019;57(1):57-58.
55. Mancini R. Implementing a Standardized Pharmacist Assessment and Evaluating the Role of a Pharmacist in a Multidisciplinary Supportive Oncology Clinic. *Journal of Supportive Oncology.* 2012;10(3):99-106.
56. Atayee RS, Sam AM, Edmonds KP. Patterns of Palliative Care Pharmacist Interventions and Outcomes as Part of Inpatient Palliative Care Consult Service. *Journal of Palliative Medicine.* 2018;21(12):1761-1767.
57. Naidu D, Jones K, Kanyer D, Hausdorff J. Palliative care pharmacist interventions in a community hospital. *Am J Health Syst Pharm.* 2018;75(13):933-936.
58. Ma JD, Tran V, Chan C, Mitchell WM, Atayee RS. Retrospective analysis of pharmacist interventions in an ambulatory palliative care practice. *Journal of Oncology Pharmacy Practice.* 2016;22(6):757-765.
59. Yamada M, Matsumura C, Jimaru Y, Ueno R, Takahashi K, Yano Y. Effect of continuous pharmacist interventions on pain control and side effect management in outpatients with cancer receiving opioid treatments. *Biological and Pharmaceutical Bulletin.* 2018;41(6):858-863.
60. Ise Y, Morita T, Katayama S, Kizawa Y. The activity of palliative care team pharmacists in designated cancer hospitals: A nationwide survey in Japan. *Journal of Pain and Symptom Management.* 2014;47(3):588-593.
61. Chen J, Lu XY, Wang WJ, et al. Impact of a clinical pharmacist-led guidance team on cancer pain therapy in China: a prospective multicenter cohort study. *J Pain Symptom Manage.* 2014;48(4):500-509.
62. Pawłowska I, Pawłowski L, Lichodziejewska-Niemierko M. The role of a pharmacist in a hospice: A nationwide survey among hospice directors, pharmacists and physicians. *European Journal of Hospital Pharmacy.* 2016;23(2):106-112.
63. Edwards Z, Bennett MI, Blenkinsopp A. A community pharmacist medicines optimisation service for patients with advanced cancer pain: a proof of concept study. *International Journal of Clinical Pharmacy.* 2019.
64. Wilby KJ, Mohamad AA, Alyafei SA. Evaluation of clinical pharmacy services offered for palliative care patients in Qatar. *Journal of Pain and Palliative Care Pharmacotherapy.* 2014;28(3):212-215.
65. Geum MJ, Ahn JH, Kim JS, et al. Interprofessional Collaboration Between a Multidisciplinary Palliative Care Team and the Team Pharmacist on Pain

Management. *American Journal of Hospice and Palliative Medicine.* 2019;36(7):616-622.
66. Lee J, McPherson ML. Outcomes of recommendations by hospice pharmacists. *Am J Health Syst Pharm.* 2006;63(22):2235-2239.
67. Wilson S, Wahler R, Brown J, Doloresco F, Monte SV. Impact of pharmacist intervention on clinical outcomes in the palliative care setting. *Am J Hosp Palliat Care.* 2011;28(5):316-320.
68. JAMES D. TOOMBS MD, and LEE A. KRAL, PHARM.D. Methadone Treatment for Pain States. *American Family Physician* 2005;71.
69. Methadone Dosing Recommendations for the Treatment of Chronic_Pain. Published 2016. Accessed March 2, 2020.
70. Association ACP. American Chronic Pain Association Published 2008. Accessed 2019, September
71. Joan Harrold MD, M.P.H.,1 ELIZABETH RICKERSON, B.A.,2 JANET T. CARROLL, M.S.N., R.N., C.H.P.N.,3 JENNIFER MCGRATH,4 KNASHAWN MORALES, Sc.D.,5 JENNIFER KAPO, M.D.,6 and DAVID CASARETT, M.D., M.A.7. Is the Palliative Performance Scale a Useful Predictor of Mortality in a Heterogeneous Hospice Population? 2005;8.
72. Palliative performance scale. Accessed 05/01, 2020.
73. Prevention CfDCa. Calculating_total_daily_dose. Accessed 05/18, 2020.
74. WHO. WHO Collaboration Center for Drug Statistics Methodology https://www.whocc.no/ddd/definition_and_general_considera/. Accessed 06/08, 2020.
75. WHO. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD. https://www.who.int/classifications/atcddd/en/. Accessed August, 18, 2020.
76. WHO. WHO Collaboration Centre for Drugs Statistics Methodology https://www.whocc.no/atc_ddd_index/. Accessed 06/08, 2020.
77. Mercadante S, Bruera E. Methadone as a First-Line Opioid in Cancer Pain Management: A Systematic Review. *J Pain Symptom Manage.* 2018;55(3):998-1003.
78. Hanna V, Senderovich H. Methadone in Pain Management: A Systematic Review. *J Pain.* 2020.
79. Marilyn J. Field and Christine K. Cassel ECoCatEoL, Institute of Medicine *Approaching Death: Improving Care at the End of Life.*
80. Parker J. Experts Share Strategies to Reduce Hospice Medication Costs. Hospice news Web site. https://hospicenews.com/2019/07/07/experts-share-strategies-to-reduce-hospice-medication-costs%EF%BB%BF/. Published 2019. Accessed December 7, 2020.
81. Chary S. Methadone for pain management Past, present and future. *Indian Journal of Palliative Care.* 2018;24(5):6-9.
82. ASHP guidelines on pharmacist role in hospice and palliative care. 2016.
83. Palat G, Chary S. Practical Guide for Using Methadone in Pain and Palliative Care Practice. *Indian journal of palliative care.* 2018;24(Suppl 1):S21-S29.
84. Hawley P, Liebscher R, Wilford J. Continuing methadone for pain in palliative care. *Pain Res Manag.* 2013;18(2):83-86.

85. Gagnon B, Almahrezi A, Schreier G. Methadone in the Treatment of Neuropathic Pain. *Pain Research and Management.* 2003;8:236718.
86. Commission MPA. Healthcare Spending and the Medicare Program. Published 2020. Accessed 9, August, 2020.
87. Rome RB, Luminais HH, Bourgeois DA, Blais CM. The role of palliative care at the end of life. *Ochsner J.* 2011;11(4):348-352.
88. Holdcroft JRA. Gender differences and pain medication. *Women's Health* 2009;5(1):79-88.
89. Carol S Weisse P, Paul C Sorum, MD, PhD, Kafi N Sanders, BS, and Beth L Syat, BS. Do Gender and Race Affect Decisions About Pain Management? *J Gen Intern Med.* 2001:211-217.
90. Franco De Conno CRaCBRaPCOU, National Cancer Institute of Milano, Milan. Opioid purchases and expenditure in nine western European countries: 'Are we killing off morphine?'. *Palliative Medicine.* 2005.
91. Neumann AM, Blondell RD, Jaanimägi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis.* 2013;32(1):68-78.

APPENDICES

Appendix 1: Instrument #1 – Pharmacist Data Collection tool

DeltaCare patient ID: ________________ Date of admission: ________________

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Instrument #1 – Pharmacist Data Collection

Duquesne study ID: _______________
Type of hospice: ☐ Home ☐ Nursing home ☐ Assisted living ☐ Inpatient
Terminal indications/diagnoses: ______________________________________
Type of pain (**select all that apply**): ☐ Nociceptive ☐ Neuropathic
Current pain medication regimen (medication/dose/schedule):
____
____

Pain intensity at admission (on a scale of 1 to 10): _______
Palliative prognosis score at admission: _______

Which of the following potential indications for methadone use are present? (**select all that apply**)
☐ Neuropathic pain ☐ Morphine allergy ☐ High opioid tolerance ☐ Refractory to other opioids ☐ Severe renal impairment ☐ Other:
____

Which of the following contraindications/precautions for methadone are present? (**select all that apply**)
☐ Clinically unstable ☐ Limited prognosis (<5 days) ☐ QTc prolongation/structural heart disease ☐ Severe liver impairment ☐ Obstructive sleep apnea ☐ Substance use disorder ☐ Electrolyte abnormalities ☐ High fall potential ☐ Use of other long-acting CNS depressant included in current medication regimen
☐ Drug interactions (if so, list which one(s)): ________________________________
☐ Other: ____

Was a recommendation for methadone provided? ☐ Yes ☐ No

If yes, what recommendation was provided:
☐ Switch to methadone as maintenance treatment
☐ Addition of methadone as adjunctive/adjuvant treatment
☐ Discontinue methadone previously prescribed
☐ Other: ______________________________________

Appendix 2: Instrument #2 – Researcher Data Collection tool

DeltaCare patient ID: _______________

Instrument #2 – Researcher Data Collection

Duquesne study ID: ________________
Age (in years): ______________ Sex (M/F): __________ Race/ethnicity: __________
Height: __________Weight: __________
Allergies: ____

Days since hospice admission: _______
Comorbidities: ____
____
PEG tube (Y/N): __________Dysphagia (Y/N): __________
Nutritional status: _________________________
Renal function: __________ Hepatic function: __________

Pain medications the patient trialed prior to admission:
____
____
____

Morphine milligram equivalents (MME) patient was on prior to admission: __________
Pain control prior to admission: ☐ Mild ☐ Moderate ☐ Severe

Morphine milligram equivalents (MME) patient on currently: _______________
Current pain control: ☐ Mild ☐ Moderate ☐ Severe
Current palliative prognosis score: ______________

Was the pharmacist recommendation for methadone accepted? ☐ Yes ☐ No ☐ NA
If yes, what day of the week was methadone recommended? ______________
If yes, how many days after admission was recommendation implemented? __________

If yes, was the dose/frequency recommended implemented? ☐ Yes ☐ No
Calculations for MME:

OPIOID (doses in mg/day except where noted)	CONVERSION FACTOR
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Appendix 3: Examples of categorization of variables

Terminal indication/diagnosis	**Indication/ diagnosis category (1=cancer, 2=dementia, 3=cardiovascular, 4=respiratory, 5=liver, 6=kidney, 7=neurodegenerative, 8=other)**
▪ Sepsis	8
▪ Alzheimer's	2
▪ ESRD	6
▪ Parkinson's	7
▪ Alzheimer's	2
▪ Cardiac arrhythmia	3
▪ Amyloidosis	8

Pain medication	**Med category1 (1=opioid, 2=NSAID, 3=APAP, 4= gabapentinoid, 5=other)**
▪ Morphine	1
▪ APAP	3
▪ Pregabalin	4
▪ Fentanyl	1
▪ Oxycodone	1
▪ Methyl Salicylate	5
▪ Ibuprofen	2
▪ Hydrocodone/APAP	1, 3

Allergies	**Allergy category (0=none, 1=opioid, 2=antibiotic, 3=topical, 4=other)**
▪ PCN	2
▪ codeine, PCN, oxycodone	1, 2
▪ morphine, amlodipine	1, 4
▪ Crestor, sulfa	2, 4
▪ Adhesive tape, nickel, morphine, aluminum, ASA, azithromycin, loratadine	1, 2, 3, 4
▪ NKA	0

Comorbidities	Comorbidity category (1=cancer, 2=dementia, 3=cardiovascular, 4=respiratory, 5=liver, 6=kidney, 7=endocrine, 8=psychiatric, 9=GI, 10=neurological, 11=other)
▪ a fib, multivalvular regurgitation, CKD, hypoxemia	3, 4, 6
▪ cervicalgia, carpal tunnel, oxygen dependent, underweight, low back pain, anxiety, GERD, chronic laryngitis, emphysema, hernia, HTN, resp failure	3, 4, 8, 9, 11
▪ HTN, COPD, dementia, DM2, hypothyroid	2, 3, 4, 7
▪ DVT, PE, HTN, cerebral atherosclerosis	3, 10
▪ clotting disorder, ascites, OA, osteopenia	3, 5, 11
▪ CKD stage 3, HTN, TIA	3, 6, 10

Appendix 4: List of DDD values

Medications with DDD values

Inhal: Inhalation, O: Oral route of administration, P: Parenteral route of administration, N: Nasal route of administration, R: Rectal route of administration

Pain		
NSAIDS	**DDD**	**Route of administration**
celecoxib	0.2 g	O
diclofenac	0.1 g	O, P, R
etodolac	0.4 g	O
ibuprofen	1.2 g	O
indomethacin	0.1 g	O
ketorolac tromethamine	30 mg	O, P
naproxen	1.2 g	O
naproxen sodium	0.5 g	O
piroxicam	20 mg	O
meloxicam	15 mg	O, P, R
sulindac	0.4 g	O, P, R
Analgesics	**DDD**	**Route of administration**
APAP	3 g	O
etodolac	0.4 g	O
acetylsalicylic acid	3 g 1 g	O P
Opioids	**DDD**	**Route of administration**
buprenorphine	1.2 g	In the data 15mcg/hr (patch)
codeine sulfate	0.1 g	
fentanyl	0.6 g 1.2 g	N, SL TD
hydromorphone HCl	20 mg 4 mg 4 mg	O P R
methadone HCl	25 mg	O, P
morphine sulfate	0.1 g 30 mg 30 mg	O P R
oxycodone	75 mg 30 mg	O P
tapentadol HCl	0.4 g	O
tramadol HCl	0.3 g	O, P, R

Pulmonary	DDD	Route of administration
budesonide	0.8 mg 0.8 mg 1.5 mg	Ihal. Aerosol Inhal. Powder Inhal. Solution
fluticasone propionate	0.2 mg	N
mometasone furoate	0.2 mg	N
ipratropium bromide	0.12 mg 0.3 mg 0.3 mg	Inhal aerosol Inhal powder Inhal sol
ipratropium bromide	0.24mg	N
tiotropium bromide	10 mcg	Inhal powder
umeclidinium bromide	55 mcg	Inhal powder
oxymetazoline HCl	0.4 mg	N
salbutamol (albuterol)	0.8 mg 10 mg	Inhal aerosol, powder Inhal solution
terbutaline sulfate	15 mg	O, P
theophylline anhydrous	0.4 g	O, P, R
tiotropium bromide	10 mcg 5 mcg	Inhal powder Inhal solution
pseudoephedrine	0.24 g	O
phenylephrine	40 mg	O
beclomethasone dipropionate	0.4 mg	N

Anticoagulants	DDD	Route of administration
apixaban	10 mg	O
cilostazol	0.2 g	O
clopidogrel bisulfate	75 mg	O
enoxaparin sodium	2 TU (time unit)	P
prasugrel HCl	10 mg	O
rivaroxaban	20 mg	O
ticagrelor	0.18 g	O
warfarin sodium	7.5 mg	O, P
heparin	10 TU	P

Medications without DDD values

Medications
albuterol sulfate
arformoterol tartrate
azelastine HCl/fluticasone propionate
albuterol sulfate
budesonide/formoterol fumarate
fluticasone furoate/umeclidinium bromide/vilanterol trifenat
fluticasone propionate/salmeterol xinafoate
formoterol fumarate
ipratropium bromide
ipratropium bromide/albuterol sulfate
levalbuterol HCl
levalbuterol tartrate
mometasone furoate
mometasone furoate/formoterol fumarate
terbutaline sulfate
theophylline anhydrous
tiotropium bromide
tiotropium bromide/olodaterol HCl
umeclidinium bromide
umeclidinium bromide/vilanterol trifenatate