**Curriculum Vitae (C.V.)**

**Aida Kuzucan, PharmD, PhD**
Baltimore, Md • aidakuzucan@gmail.com • Linkedin

## Education

- Doctor of Philosophy (PhD)
  University of Maryland, Baltimore, Md
  Pharmaceutical Health Services Research Department
  May 2021
    - Dissertation: Optimizing pain management in long-term care nursing home Medicare beneficiaries- a trajectory model approach.
- Doctor of Pharmacy (PharmD)
  University of Maryland, Baltimore, Md
  May 2015
- Bachelor of Arts, Biological Anthropology (BA)
  University of California, San Diego, La Jolla, Ca.
  March 2009

## Professional Experience

Graduate Research Assistant/ T32 Epidemiology of Aging Fellow • University of Maryland, School of Pharmacy • Baltimore, Md • August 2016-Current

- Co-authored, co-designed, and served as project manager for a 1.6 million-dollar NIH awarded R01 grant on the effect of antipsychotic use reduction policies on various health-related outcomes in nursing home residents.
- Executed, managed, and served on a team for various epidemiologic, comparative-effectiveness, and outcomes studies focused on individuals with substance use related disorders (SUD), Chronic obstructive pulmonary disorder (COPD), cancer, chronic pain, and Alzheimer's and related-dementias (ADRD).
- Led multidisciplinary teams in literature reviews and discussions to identify optimal methods for defining and identifying measures that would mirror real-world practice and minimize misclassification.
- Managed the purchase and/or ascertainment of multiple data sources including CCW Medicare and Medicaid claims data, Minimum Dataset 3.0, Nursing Home Compare data, Health Services Cost Review Commission data, and MarketScan.
- Trained and mentored new team members, interns, new graduate students, and clinical and research consultants on epidemiological and comparative-effectiveness methodology.
- Worked with a team to analyze, compile, and distribute annual county-specific epidemiologic reports describing alcohol and drug-related hospitalizations for all Maryland's departments of health.
- Provided literature and helped design a graduate level patient centered outcomes and comparative effectiveness research course for the pharmaceutical health services research department.

- Facilitated a comparative effectiveness research (CER) certificate program on assessing and synthesizing CER literature for pharmaceutical industry employees.
- Provided an invited lecture on introductory substance abuse epidemiology to pharmacy students.

Graduate Student Intern • Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) • Alexandria, VA • June 2016 – Jan. 2017

- Served as project coordinator for this multi-stakeholder consortium.
- Leveraged existing Sentinel distributed research network resources for comparative effectiveness research and active surveillance on biosimilars and biologics.
- Compiled and assessed literature for discussion on optimal measure operationalization.

Consultant• Avelere Health, LLC. • Baltimore, Md. • Nov. 2014 – Mar. 2015

- Worked on a multidisciplinary team compiling and evaluating both published and grey literature evidence to justify COPD quality measures for a health care organization.

Student Pharmacist Intern • Walgreens Pharmacy• Baltimore, Md• Aug. 2012 – Jan. 2014

- Interfaced with patients, clinicians, and insurance providers to ensure safe and affordable medications for the consumer.

Researcher/Clinical Coordinator • John Tu & Yuen Center for Functional Onco-Imaging University of California, Irvine • Irvine, Ca. • Aug. 2009 – Jul. 2011

- Work at center focused on assessing the comparative utility of 3 Tesla vs. 1.5 Tesla magnetic resonance imaging in neoadjuvant chemotherapy for breast cancer.
- Collected data from medical charts and patients, translated data into datasets, facilitated appointments and medical tests accordingly to protocols.
- Data analyses from one-year as a researcher resulted in one primary and two coauthored publications.

Co-teacher • Rancho Santiago Canyon College, • Santa Ana, Ca. • Jan. 2010 – Jun. 2011

- Designed and provided supplementary lectures to reinforce introductory cellular and molecular biology topics for science majors.

## Publications

- **Kuzucan A,** Lapane K, Wang Y, Brandt N, Perfetto E, and Simoni-Wastila L. Hospitalizations and constipation in long-term care nursing home residents with varying opioid induction dosing patterns and trajectories. *JAMDA* 2020, in review.

- **Kuzucan A,** Lapane K, Wang Y, Brandt N, Perfetto E, and Simoni-Wastila L. Long-term care nursing home resident characteristics associated with varying opioid induction dosing patterns and trajectories. *PAIN* 2020, in review.
- **Kuzucan A,** Lapane K, Wang Y, Brandt N, Perfetto E, and Simoni-Wastila L. Trends in Opioid and Opioid-Pain Adjuvant Combination Prescribing Among Cancer, Hospice, Chronic Pain, and Demented Stays in Long-Term Care (LTC), 2011 -2015. *JAGS* 2020; in review.
- Le T, Flemming S, Dizik A, **Kuzucan A,** and Simoni-Wastila L. Query mandates in prescription drug monitoring programs reduce opioid use among commercially insured patients newly diagnosed with cancer. *Cancer*. 2020; in review.
- **Kuzucan A,** Powers JH, Doshi P. Antibiotics approved for marketing in populations specifically excluded from premarketing trials, 1999-2018. *Mayo Clinic Proceedings* 2020; accepted for publication.
- Doshi P, **Kuzucan A**, Powers JH. Communication of nonefficacy benefits of new drugs approved on the basis of noninferiority trials alone: cohort study of FDA and sponsor communication, 2011-2017. *JAMA internal medicine*. 2019 May 1;179(5):719-21.
- **Kuzucan A**, Chen JH, Bahri S, Mehta RS, Carpenter PM, Fwu PT, Hon JY, Hsiang DJ, Lane KT, Butler JA, Feig SA. Diagnostic performance of magnetic resonance imaging for assessing tumor response in patients with HER2-negative breast cancer receiving neoadjuvant chemotherapy is associated with molecular biomarker profile. *Clinical breast cancer*. 2012 Apr 1;12(2):110-8.
- Moon WK, Shen YW, Huang CS, Luo SC, **Kuzucan A**, Chen JH, Chang RF. Comparative study of density analysis using automated whole breast ultrasound and MRI. *Medical physics*. 2011 Jan;38(1):382-9.
- Chen JH, Bahri S, Mehta RS, **Kuzucan A**, Yu HJ, Carpenter PM, Feig SA, Lin M, Hsiang DJ, Lane KT, Butler JA. Breast cancer: evaluation of response to neoadjuvant chemotherapy with 3.0-T MR imaging. *Radiology*. 2011 Dec;261(3):735-43.
- Bahri S, Chen JH, Yu HJ, **Kuzucan A**, Nalcioglu O, Su MY. Can dynamic contrast-enhanced MRI (DCE-MRI) predict tumor recurrence and lymph node status in patients with breast cancer? *Annals of oncology*. 2008 Apr 1;19(4):822-4.

## Posters/Presentations

- **Kuzucan A** and Simoni-Wastila L. When is competing risk analysis appropriate? Weighing bias from censoring and analytics. T32 Epidemiology of Aging Seminar, October 2020, Online.
- **Kuzucan A** and Simoni-Wastila L. Trends in opioid use alone and in combination with adjuvant medications during long-term care nursing home (LTC) stays, 2011–2015. AHSR Annual Meeting, October 2020, Online.
- Le T, Fleming D, **Kuzucan A**, and Simoni-Wastila L. Prescription Drug Monitoring Program Rigor and Opioid Use In Patients with Cancer. AHSR Annual Meeting, October 2020, Online.

- **Kuzucan A**, Simoni-Wastila L. Factors Associated With Opioid Use Among Long-stay Nursing Home Residents. Poster presentation at ISPE's 36th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, September 2020, Online.
- Holmes SD, **Kuzucan A,** Brandt N, Qato D, Zarowitz B., Wastila L. The association of antipsychotic use with care transitions among long-term care residents. Poster presentation at the Annual Meeting of the American Geriatrics Society, May 2020, Long Beach, CA.
- **Kuzucan A**, Flemming S, Simoni-Wastila L. Odds Of Discharge To Substance Abuse Treatment Or Psychiatric Care After Hospitalization for Alcohol or Drug Poisonings, Maryland 2016-2017. Poster presentation at the Addiction Health Services Research Conference, October 2019, Long Beach, Ca.
- Flemming S, **Kuzucan A**, Simoni-Wastila L. Cocaine and Opioid Polysubstance-Related Hospital Events on the Rise in Maryland, 2016-2018.Podium Presentation at the Addiction Health Services Research Conference, October 2019, Long Beach, Ca.
- **Kuzucan A**, Fleming S, Simoni-Wastila L. Predictors of in-hospital Psychiatric Care among Alcohol- and Drug- related Hospitalizations in Maryland, 2016. Poster presentation at 35th ISPE International Conference on Pharmacoepidemiology and Therapeutic Risk Management August 2019, Philadelphia, PA.
- **Kuzucan A**, Simoni-Wastila L. Unintentional and suicidal opioid overdose in Medicare beneficiaries. Poster presentation at ISPOR, May 2019, New Orleans, La.
- **Kuzucan A**, Qato DM, Simoni-Wastila L. Characteristics Associated with Intentional Opioid Overdose in Medicare Beneficiaries. Poster presentation at October 2018, AHSR 2018-Savanah, Ga.
- **Kuzucan A**, Simoni-Wastila L. Substance Use Disorders and Overdose Events in Medicare Beneficiaries. Poster presentation at 33rd ISPE International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2018, Montreal, Canada.
- Tham L, **Kuzucan A**, Wang Y, and Simoni-Wastila L. Validating the Latent Construct of Problematic Opioid Use Among Medicare Beneficiaries, ICPE Annual Meeting, August 2018, Prague, Czech Republic.
- **Kuzucan A**, Simoni-Wastila L. Comorbidities, Medication Use, and Overdose: A Snapshot of Medicare Beneficiaries with Substance Use Disorders. Podium presentation at AcademyHealth Behavioral Health Interest Groups Meeting, April 2017, New Orleans, LA.
- **Kuzucan A**, Moyo P, Simoni-Wastila L. Emergency Department Visits and Hospitalizations Before and After Prescription Drug Monitoring Implementation in Maryland: Does Policy Impact Differ by Age? Poster presentation at AHSR 2016, October 2016, Seattle, Wa.
- **Kuzucan A**. Relative efficacy of Abreva and acyclovir formulations in the treatment of cold sores: Should we keep Abreva on formulary? Formulary team presentation at Cumberland Health Systems P&T committee, July 2013, Cumberland, MD.
- Mehta R, Chen J, Bahri S, Carpenter P, **Kuzucan A**, Yu H, Nalcioglu O. Su M. Abstract P2-02-11: Evaluation of Tumor Response using 3T Breast MRI Following

Neoadjuvant Albumin-Bound Paclitaxel and Carboplatin with Bevacizumab or Trastuzumab. Presentation at Breast Cancer Symposium at 33rd Annual CTRC-AACR, December 2010, San Antonia, TX.

- **Kuzucan A**, Chen J, Mehta R, Bahri S, Capenter P, Yu H, Nalcioglu O, and Su M. Diagnostic Performance of MRI for Assessing Tumor Response in Her -2 negative Breast Cancer Receiving Neoadjuvant Chemotherapy. Poster presentation at 19th Annual Meeting & Exhibition of International Society for Magnetic Resonance in Medicine, May 2010, Montreal, Canada.

## Awards/Professional Service

- (2018-Present) T32 Epidemiology of Aging Fellow
- (2017-2018) President - ISPOR at UMB
- (2019-Present) Leadership Team Member - ISPOR Aging SIG
- (2016-Present) Leadership Team Member - ISPOR Patient SIG
- (2016) Harris Zuckerman Scholarship Awardee
- (2016) Early Career Investigator Award, National Institute on Drug Abuse (NIDA) at the Addiction Health Services Conference (AHSR)
- (2016-2017) VP- ISPE at UMB
- (2015-2016) Dr. Arthur Schwartz Memorial Scholarship Awardee
- (2013-2014) VP - A Bridge to Academic Excellence Outreach Group
- (2012) Academic Student of the Month - Rho Chi & Phi Lamda Sigma at UMB
- (2012) Leadership Student of the Month - Rho Chi & Phi Lamda Sigma at UMB
- (2012) Participant- Dean's Seminar Series (by invitation only) at UMB
- (2012) Participant- Leadership in HIV Summit - Jacques Initiative
- (2007-2008) Vice President - UCSD Student Government
- (2005-2007) College Senator - UCSD Student Government

## Current Certificates and Licenses

- Pharmacist license No. 23818
- Pharmacy Immunization Delivery Certification Cardiopulmonary Resuscitation Certificate
- HIPAA Certified
- CITTI Certified

**ABSTRACT**

Problem statement: While much needed clinical research has emphasized appropriate opioid stewardship in the general population, the needs of long-term nursing home care (LTC) residents remain largely ignored.

Methods: This dissertation identified emerging trends in opioid therapy and initial opioid dosing patterns among LTC Medicare beneficiaries using Medicare Parts A, B and D claims, the Minimum Data Set 3.0 (MDS) and LTCFocus datasets. Aim 1 is a repeat cross-section study using resident and facility adjusted generalized estimating equations (GEE) to examine patterns of opioid use alone and in conjunction with pain-adjuvant medications among general, hospice, cancer, non-cancer chronic pain and dementia-related LTC stays from 2011 to 2015. Aim 2 identifies common patterns of average morphine equivalent daily dosing (MEDD) across six 30-day intervals starting with the first opioid prescription using latent class growth modeling (LCGM). Multivariate multinomial regression quantifies associations between different opioid use patterns over time and resident characteristics. Aim 3 accesses the odds of falls among residents with the highest probability of belonging to each of the commonly identified opioid dosing patterns with a facility clustered GEE model.

Results: From 2011 to 2015, adjusted analyses found no constant significant changes in dose, duration, or frequency of opioid use. Increased use of anticonvulsant and skeletal muscle relaxants in opioid-related stays, particularly among residents with dementia, were found. LCGM identified four common opioid dosing patterns; extended high, short-term, intermittent and restart. Almost half of LTC residents received extended high opioid dosing. Multinomial regression found significant associations between sex, race,

U.S. geographical region, pain diagnosis and receipt of other pain treatments with receipt of extended high dose therapy. Fall odds were found to be similar in the extended high and short-term groups. Models did find increased odds of falls in groups with less opportunity to develop tolerance (i.e., the restart and intermittent groups). Findings were not consistently significant in stratified analyses.

Conclusions: Opioid use varies by resident characteristics. Opioid dosing varies over the course of therapy. More research on what factors lead to decisions regarding pain treatment and the impact of opioid dosing strategies on health-related outcomes are warranted.

# Optimizing Pain Management in Medically Complex Long-Term Care Residents

by
Aida Kuzucan

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2021

# ACKNOWLEDGEMENTS

This work would not have been possible without the unwavering support of my mentors, my friends, and my family.

To my mentor, Dr. Linda Wastila: thank you for making me into a public health researcher, for guiding me through this whole process, for encouraging me to ask questions, for teaching me to focus on one question at a time, and for being my personal and professional support. I may be finishing my time at University of Maryland, but you are stuck with me.

To Dr. Eleanor Perfetto, Dr. Yan Wang, Dr. Kate Lapane, and Dr. Nicole Brandt: thank you for your time, your understanding, and your expertise during this process. You each provided me invaluable advice, direction, and encouragement throughout this work.

To O'Mareen, Maya, Priyanka and Laura: thank you for teaching me, supporting me, and being my friends.

To my mom (Ayşe) and my sister (Aylin): Thank you for inspiring me with your strength and brilliance. You both are proof of what strong, smart, and independent women can do.

To my husband (Ian) and my son (Aydın); thank you for your love, understanding, and support during this process. Ian, you challenge me to be smarter, better, and more socially conscious and I love you for it. Aydın, Mommy is done and can play now.

To Al, Eileen, and Caitlin; thank you for being a support to me, Aydin and Ian. We are so lucky to have you.

And finally, to my father (Alpdoğan) and all the other people who can no longer live without around the clock nursing care. I see you. I care about you. And I will continue to dedicate my time to make your lives better.

TABLE OF CONTENTS

**LIST OF TABLES**

**LIST OF FIGURES**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Antidepressant |
| AC | Anticonvulsant |
| AGS | American geriatrics society |
| ANOVA | Analysis of variance |
| BIMS | Brief interview for mental status |
| CCW | Chronic conditions warehouse |
| CMS | Centers for Medicare and Medicaid Services |
| CN | Certified nursing assistant |
| CN | Central nervous system |
| CPS | Cognitive performance scale |
| ER | Emergency room department |
| GEE: | Generalized Estimating Equation |
| HIV/AIDs | Human immunodeficiency virus/ Acquired immunodeficiency syndrome |
| LCGM | Latent class growth modeling |
| LP | Licensed practical nurse |
| LTC | long-term care |
| MANCOV | Multivariate analysis of covariance |
| MEDD | Morphine milligram equivalent daily dose |
| MCBS | Medicare current beneficiary survey |
| MDS | Minimum dataset |

| | |
|---|---|
| MR | Skeletal muscle relaxant |
| NCC | Non-cancer chronic pain |
| OREC | original reason for entitlement |
| PRN | Medication use is as needed |
| RN | Registered nurse |
| SD | Standard deviation |
| SEM | System equation modeling |
| SNF | Skilled nursing facility |
| TROUP | Trends and Risks of Opioid Use for Pain study |

# CHAPTER 1: INTRODUCTION

## 1 Problem Statement

While much needed clinical research has emphasized appropriate opioid stewardship in the general population, the needs of long-term nursing home care (LTC) residents remain largely ignored. A lack of practical alternatives makes opioid medications the preferred pharmacological treatment for non-malignant chronic and acute pain.[1–4] Older age, frailty, concurrent diseases, and polypharmacy often seen among LTC residents might result in (at relatively similar opioid doses and durations) increased opioid-related risks.[5,6] No known study has examined opioid dosing patterns, specifically initial dose and escalation rates, across multiple time points in the LTC setting and its relationship with falls, despite their increased risk for adverse outcomes of both opioid over- and under- treatment.

## 2 What is LTC?

Nursing homes provide both skilled nursing facility services (SNFs) and long-term care (LTC) services. Varying needs and care expectation have led Center for Medicare, and Medicaid Services (CMS) quality metrics to distinguish between residents receiving primarily SNF and LTC services.[7] SNF services typically provide rehabilitation services over a short period of time immediately following a hospitalization. Discharge is the primary aim of SNF stays. Medicare pays for up to 120 SNF stay days under Medicare part A. In contrast, LTC services aim to help residents in their day-to-day care which includes the management of chronic conditions such as pain. Resident morbidity limits the feasibility of discharge in this population.[8,9] Annually, 794,000 people in the United States are LTC residents.[9]

While several studies in the nursing home population have used linked survey and claims data, identification of residents with pain have relied solely on minimum dataset surveys regarding pain. Prior studies suggest that between 45% and 80% of residents experience pain that effects their ability to function or quality of life.[10] Definitions for persistent pain in MDS are operationalized as two consecutive (usually 90 to 120 days apart) surveys that indicated the presence of at least some pain.[5,6,10–12] Depending on the time frame and cohort source, estimates of non-malignant persistent pain among nursing home residents have ranged from 19.5% to 65%. In a study of residents participating in the 2009 Medicare Current Beneficiary Survey (MCBS), Shen and associates' linked data analysis found that 60% of residents with uninterrupted nursing homes stays between two minimum data set (MDS) assessments had persistent pain.[11] Of note, residents with diagnoses of cancer were not excluded from the analysis. A 2007 to 2009 MDS study of residents, that did exclude residents on hospice and with cancer, found non-cancer chronic pain (NCCP) in 25.2% of nursing home residents.[5] Requiring 2 MDS estimates to define non-malignant persistent pain implies residents lived in the nursing home for at least 90 days. Still, only one study described additional criteria to limit their analyses to LTC residents. Among residents with nursing home stays longer than 100 days, including those with cancer and hospice diagnoses, Hunnicut and associates identified a persistent pain prevalence of 19.5%.[6]

Studies outside of the nursing home population often focus on diagnosis codes for identifying non-malignant persistent pain. The TROUP (Trends and Risks of Opioid Use for Pain) study designed to assess trends in and risks of opioid therapy in contrasting pain

populations used a list of ICD-9-CM codes for possible non-malignant persistent pain conditions and opioid use longer than 3 months as an indication of non-malignant persistent pain. Four categories of possible non-malignant persistent pain were identified: back pain, arthritis/joint pain, headache/migraine, and HIV/AIDS pain.[13] While the diagnoses alone don't indicate chronic disease, multiple diagnoses at least 3 months apart would be consistent with definitions of non-malignant persistent pain. No known study in the nursing home or LTC population has incorporated theses diagnoses codes in analyses estimating the prevalence of non-malignant persistent pain. This study will use recent data, exclude appropriate populations, and use a validated algorithm to identify LTC residents to provide updated estimates of non-malignant persistent pain in LTC residents.

4 Characteristics of Long-term Care Residents Receiving Opioid Therapy

Previous studies accessing associations between race and opioids use patterns have relied of survey responses known to under count individuals outside of the non-Hispanic race.[14] Still, white non-Hispanic race has consistently been associated with any, higher dose, and longer acting opioid use in LTC in the United states.[10,15–17] For example, a cross sectional study of all long-stay U.S. nursing home residents with an assessment and Medicare Part D enrollment in 2008, found the proportion of prescription opioid or NSAID use was 3.6 to 12.8% greater in non-Hispanic white residents compared residents identified as other races ($p<0.0001$).[10]

Recent studies accessing associations with sex, cognitive impairment, and use of other pain adjuvant medications with opioid use have been limited to the first 120-days of nursing home stays. Hunnicutt and associates found that among LTC residents in 2012, more women compared to men received opioid therapy in the first 120-days of their stay

(34.1% versus 26.8%).[6] In another study by Hunnicutt and associated in the same cohort, use of other pain medications (25.5% versus 11.0%) and nonpharmacological pain treatments (24.5% versus 9.3%) were more common in residents prescribed opioids.[16] Mehta and associates analysis of a 20% sample of Medicare beneficiaries from 2011 to 2017 found inverse associations between cognitive impairment and receipt of any, high dose, or long-term opioid therapy.[17]

5 Opioid Safety in Long-term care

Opioid use in nursing homes are associated with preventable adverse events, such as falls resulting in hospitalizations or emergency room (ER) visits and constipation.[18–21] Previous studies in older adults have found increased risks of abuse, overdose, falls, and fractures with opioid use.[2,22–26] Studies describing opioid use patterns in LTC have found variations in dose, formulations and durations of therapy.[21,22,24,25,27] This heterogeneity in use might be due to variations in pains response to opioids and the development of adverse outcomes.[2,22,25,28]

Safety risks from opioid use are greatest within a couple weeks after initiating therapy or escalating dose.[29] Yet, clear recommendations on initial dose and dose escalations are lacking. This is probably due to a lack of observational or clinical trial evidence regarding titration and initiation of opioid therapy in medically complex populations. Pain-management guidelines often recommend against use of opioids or suggest to "start low and go slow" in the general older adult and nursing home population.[2,25,30] These guidelines are focused on preventing opioid overdose and might not pertain to a population where medication administration is done by medical professionals. Studies describing how or whether these guidelines are followed in the

LTC setting are lacking. To our knowledge, no known study has evaluated the risks of opioid dose initiation and escalation patterns in LTC residents.

Residents with multiple physical and/or psychiatric comorbidities may be at higher risk for opioid exposure, including high dose opioid exposure. Studies describing the comorbidity make-up of individuals receiving opioid therapy only present the prevalence of single conditions.[15,31] It is unclear whether mental disorders or the presence of multiple physical, cognitive, or mental conditions effect opioid dosing. Also a concern, under-treatment of pain has been associated with functional decline and mental illness.[5,31–33] Among LTC residents with moderate to severe pain lasting more than 3 months, older and cognitively impaired adults are the most likely to receive no analgesic therapy, possibly due to diminished pain expression ability.[10,34]

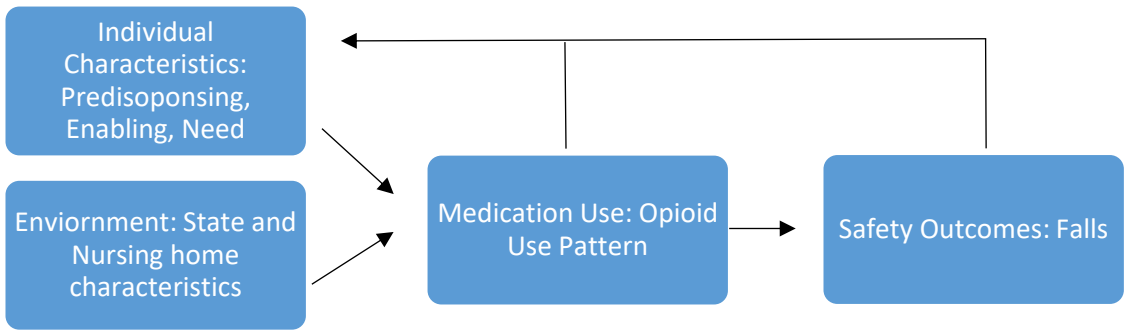
7 Significance

We hypothesize that complex LTC residents, especially those with multiple cognitive or physical impairments, will be at higher risk of receiving high dose opioids either initially or within a relatively short period of time relative to individuals with fewer co-morbid illnesses. In turn, these older and frailer complex residents may be placed at increased opioid-related safety risks.[15]

## CHAPTER 2: THEORETICAL FRAMEWORK

The conceptual framework used to guide the proposed study is Andersen's Behavioral Model of Health Services Use (Figure 1).[35] It illustrates the hypothesized factors associated with receiving varying opioid dose patterns (Aim 1 and Aim 2) and experiencing select safety outcomes (Aim 3) among LTC residents Medicare Beneficiaries. Population characteristics include: 1) predisposing factors (race, sex, other personal attributes that predispose individuals to seek care); 2) enabling factors (LTC facility characteristics, health insurance, and other factors that influence one's ability to access care); and 3) need factors (severity-of-illness and comorbidities). Originally developed to study access and utilization, the Andersen Behavioral Model has been widely used in diverse studies of substance use, mental health, older adults, and other vulnerable populations.

*Figure 1: Conceptual Framework Based on Anderson's Behavioral Model of Health Services Use.*



## CHAPTER 3: MANUSCRIPTS

### Aim 1: Trends in Opioid and Opioid-Pain Adjuvant Combination Use Among Cancer-, Hospice-, Chronic Pain-, and Dementia-Related Long-Term Care Stays, 2011-2015.

Abstract

Background/objectives: Despite high prevalence of pain and opioid use in long-term care (LTC) patients, studies describing opioid and pain-adjuvant use trends remain scant.

Design: Repeat cross-sectional using 2011-2015 data.

Setting: Medicare Beneficiary LTC stays from a random 5% national sample of Medicare claims linked to Minimum Data Set 3.0 (MDS) and nursing home characteristics data.

Participants: General, hospice, non-chronic cancer pain (NCCP), cancer, and dementia LTC patient stays with >100 custodial-care days (N=122,970).

Measurements: Opioid and opioid-pain adjuvant-therapy use trends. Opioid-use trends included annual changes in any use, high-dose, chronic, and/or therapy over ≥50% of the stay. Opioid-pain adjuvant therapy use was defined as any opioid use plus ≥1 select triptan, skeletal muscle relaxant, anticonvulsant, systemic corticosteroid, and/or antidepressant during a stay.

Results: From 2011 to 2015, analyses adjusted for facility and resident characteristics did not indicate constant or significant changes in dose, duration, or frequency of opioid use in general, hospice, cancer, NCCP, or dementia LTC stay-years. During this period, odds of opioid+skeletal muscle relaxant use increased by 81%, 26%, 75%, 114%, and 116% in the general, hospice, NCCP, cancer, and dementia LTC stay-years, respectively. Odds of opioid+anticonvulsant use also increased across stay-years, with odds in 2015 31%, 8%,

32%, 39%, and 33% greater than 2011 among general, hospice, NCCP, cancer, and dementia LTC stay-years, respectively.

Conclusions: Opioid-related stays with anticonvulsants and skeletal muscle-relaxants in all, cancer, dementia, hospice, and NCCP LTC patient stays are increasing. More research on the clinical implications of using these combinations in LTC patients is warranted.

## Introduction

Reports of pain in long-term care (LTC) nursing home residents are common despite a sizable dementia population that may have trouble communicating pain.[5,31,36,37] Depending on the time frame and population source, pain in nursing home residents is estimated to range from 19.5% to 65.0%.[5,16,31] While the reasons for and sources of pain in residents with cancer, non-cancer chronic pain (NCCP), dementia, and end-of-life care might differ, opioids remain a general pain management tool used by prescribers serving LTC residents. [38,39]

Increasing concerns driven by rising opioid overdose rates in younger, community-dwelling populations may alter how prescribers select opioids and pain adjuvants in LTC. One recent study found 17% reduced odds of any opioid or high-dose opioid (≥90 morphine equivalent milligrams daily) use during the first three months of LTC stay in 2015 compared to 2011.[17] Similar decreasing trends were seen among those with and without cognitive impairment. If these trends are also seen in other populations with pain, such as those with cancer, non-cancer chronic pain, or end-of-life care, it could indicate clinicians are non-discriminately decreasing access to opioid treatment in LTC.

This could be detrimental in LTC where undertreatment of pain, and its association with cognitive decline, functional decline, and depression, is often reported.[3,39]

Previous studies have estimated that one in three LTC residents will receive opioid therapy in the first three months of their stay.[17,36] Opioid use over an entire LTC stay as individuals become sicker or closer to death might be even higher. Opioid use is not without risks as these often older, frail, and multimorbid residents are particularly vulnerable to opioid-related sedation, falls, and respiratory depression.[1,40] Opioid regimens that include the use of pain adjuvants (e.g., anticonvulsants, antidepressants, and skeletal muscle relaxants) modulate the pain experience, potentially reducing opioid need. Outside the cancer population, studies demonstrating the benefits of specific pain adjuvant-opioid combinations are rare and inconclusive.[41,42] Studies evaluating safety-risks (such as falls and hospitalizations) associated with centrally-acting, sedating medications often find combination therapies incur additional risk.[43,44] Understanding in whom and to what extent opioid and pain-adjuvant combinations are used in the nursing-home setting are necessary to assess use, identify areas for further health-outcomes-related research, and determine a baseline for future evaluation.

The objective of this study is to expand on previous work by examining patterns of opioid use alone and in conjunction with pain-adjuvant medications over time among general, hospice, cancer, NCCP, and dementia-related LTC stays. By focusing on Medicare Part D populations, we were able to use multiple, rich data sources to calculate annual odds of varying opioid and opioid-combination use patterns while accounting for facility and resident factors that might have varied over time.

## Methods

### Study design and data source

This repeat cross-sectional study used three linked survey and health administrative databases to identify and describe trends in annual opioid use among Medicare beneficiaries living long-term in U.S. skilled nursing home facilities from January 1st, 2011 to December 31st, 2015. The chronic conditions warehouse (CCW) dataset includes all Medicare fee-for-service (FFS) institutional and non-institutional claims and enrollment/eligibility information for a random 5% sample of Medicare beneficiaries. The Minimum Data Set 3.0 (MDS) surveys include quarterly assessments describing active diagnoses and stay length. LTC focus datasets, publicly available nursing home facility-level files developed by Brown University for the "Shaping Long Term Care in America Project," includes facility-level annual files describing the health and functional status of nursing home residents and quality and management characteristics of care facilities.[45]

### Study sample

The unit of analysis for this study was LTC stay-years. To identify eligible LTC-stay-years, we first used an algorithm incorporating SNF services covered by Medicare part A and admission and discharge dates as indicated by the MDS to identify long-term stays.[46–48] A stay was defined as long-term if the total days between admission and discharge, or the last available assessment date, after subtracting days associated with SNF services was at least 100 days. Then, LTC stays were converted to LTC stay-years. LTC stay-years were defined as the time during an LTC stay that occurred in a single year. For example, a stay from July 2011 to February 2012 results in two stay-years: a 6-

month stay in 2011 and a 2-month stay in 2012. One individual could account for multiple stays and one stay could result in multiple stay-years.

Additional inclusion criteria included survival for at least three months after admission to a nursing home and continuous enrollment in Medicare Parts A, B, and D during the stay. Continuous coverage allowed for accurate identification of LTC stays and opioid use. Stays among residents reported as comatose or with Medicare Advantage coverage during the stay were excluded. From 2011 and 2015, 122,970 LTC stays and 244,343 LTC stay-years were identified for our study (Figure 2).

MDS survey data and Medicare Parts A and B claims were used to identify stays associated with residents with dementia, cancer, chronic non-cancer pain conditions and end-of-life care. Stays associated with dementia diagnosis were identified if at least one assessment during the nursing home stay reported an active dementia diagnosis (I4800_DMNT_CD). Hospice-related stays were any LTC stay after a hospice start date as reported in the hospice file in the CCW dataset. To identify beneficiaries with malignant cancers, we required at least one skilled nursing facility, inpatient claim or 2 outpatient or carrier claims with an ICD-9 diagnosis code of ICD-9 CM 140-209, 338.3.[49] Beneficiaries with non-cancer chronic pain did not identify as having malignant cancer and had at least one diagnosis for painful conditions previously identified as leading to chronic pain (Table 1).[36,50,51] Acute pain conditions expected to resolve, such as hip fracture, were not included in our NCCP definition.

*Figure 2: Development of LTC stay-years for trend analysis.*

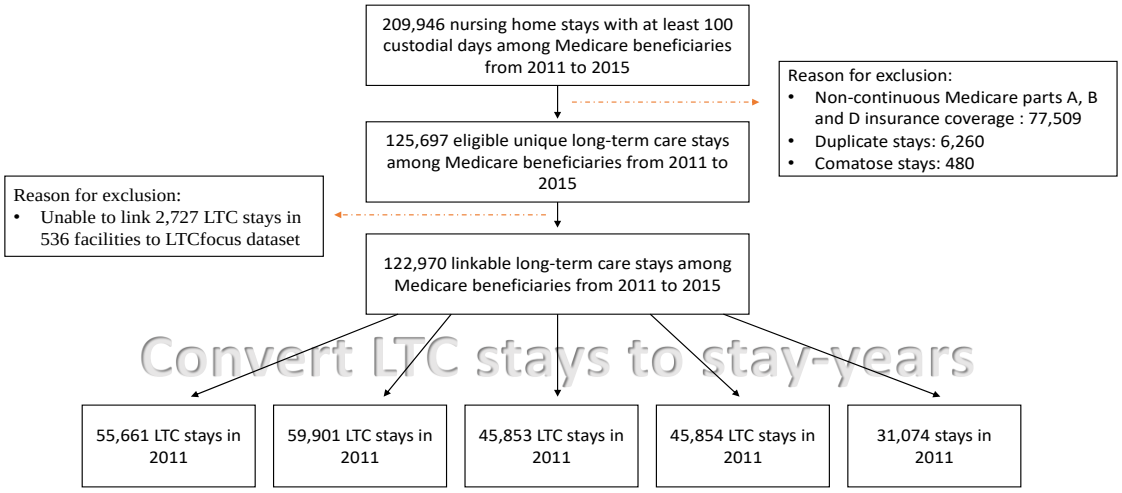



*Table 1: ICD-9 CM and ICD-10 CM codes used to define chronic painful conditions from outpatient, skilled nursing, and physician claims.* [50–52]

| Painful conditions | ICD- 9 CM Definition | ICD-10 CM Definition |
|---|---|---|
| Chronic pain | 338.0, 338.2x, 338.4 | G89.0, G89.2x, G89.4 |
| Abdominal pain | 533.4x-533.9x, 550.x-553.x, 555.x, 556.x (except 556.4), 564.1, 569.42, 577.1x, 590.0x, 789.0x | K27.4-K27.9, K40.x-K46.x, K50.x, K51.x (except K51.4x), K58.x, K62.89, K86.0, K86.1, N11.x, R10.1x-R10.8 |
| Musculoskeletal pain | | |
| Back/neck pain | 720.x-724.x | M45.x-M55.x |
| Head | 307.81, 339.x, 346.x | G43.x, G44.x |
| Limb pain | 354.4, 355.71, 729.5 | G56.4x, G57.7x, M79.6x |
| Arthritis/rheumatism/ joint pain/myalgia | 274.x, 710.xx-719.xx, 725.x-729.x (excluding 729.5 and 729.2) | M1A.x, M05.x-M08.x, M11.x-M19.x, M22.x-M25.x, M65.x-M67.x, M70.x-M71.x, M75.x-M77.x, M79.x (except 79.6x and M79.2), M94.x |
| Neuropathic pain | 53.1x, 249.6x, 250.6x, 337.1, 337.2x, 340.x, 341.9, 350.x, 351.x, 353.x-356.x, 357.81, 729.2, 951.4, 952.x, 953.x | B02.23, E08.4x, G99.0, G90.5x, G35.x, G37.9, G50.x, G54.x, G56.x(except G56.4), G54.x-G58.x (except G57.7x), G61.81, M79.2, S04.50XA, S14.x, S24.x, S34.x |

Opioid use

For each year from 2011 to 2015, we used Medicare Part D prescription drug claims to identify and describe opioid use during LTC. During each stay-year, we calculated the proportion of stay-days where opioids were supplied, the cumulative number of days opioids were supplied, and the average opioid dose per day supplied (in oral morphine equivalents). Opioid days supplied were identified using the dispensing date and days' supply.[53] While calculating days' supply, we assumed overlapping prescriptions of ≥ 1 day were used simultaneously. From these calculations, we flagged stays associated with chronic (≥ 90 days of opioid use during their stay), high dose (average daily oral morphine equivalent ≥ 90mg), and opioid saturation ≥ 50% (at least 50% of days during an individual LTC stay-year associated with opioid therapy) opioid therapies. Opioid saturation ≥ 50% is a novel measure we created to account for the possible increased risk of opioid exposure with increasing LTC stay length.

We calculated stay-year-level average, oral morphine equivalent daily dose (MEDD) by multiplying the strength per unit in milligrams by the average daily units dispensed and the oral morphine equivalent conversion (OME) conversion factor (Equation 1). OME factors were those used by the Centers for Disease Control and Prevention.[54]

*Equation 1: Equation for calculating MEDD from Medicare part D claims.*

$$\left(\frac{strength\ (mg)}{unit}\right) * \left(\frac{total\ stay-year\ units\ dispensed}{stay-year\ days'\ supply}\right) * OME\ conversion\ factor$$

Use of pain adjuvant medications

Use of pain adjuvant medications in combination or concurrently with opioids, were flagged using Medicare Part D claims. Based on previous literature and the American Geriatrics Society (AGS) clinical guidelines for pharmacological management of persistent pain in older persons, we identified and categorized the following as prescribed pain adjuvant medications: select triptans, skeletal muscle relaxants (MR), anticonvulsants (AC), systemic corticosteroids, and antidepressants (AD) (Table 2).[3,16,55] Due to our inability to reliably capture over-the -counter pain medications, acetaminophen and NSAIDs were not included in our analysis.

*Table 2: Opioid and non-opioid pain and pain adjuvant medications.* [36,55,3]

| Category | Generic drugs included |
|---|---|
| Opioids and opioid combination products | Albuphine, buprenorphine, buprenorphine combination products, codeine, codeine combination products, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, oxycodone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxymorphone, pentazocine, tapentadol, tramadol and opioid combination products |
| Triptans | eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan |
| Skeletal Muscle Relaxants (MRs) | baclofen, carisoprodol, chlorzoxazone, clonazepam, cyclobenzaprine, metaxalone, tizanidine |
| Anticonvulsants (ACs) | carbamazepine, gabapentin, pregabalin, lamotrigine |
| Systemic corticosteroids | betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone |
| Antidepressants (Ads) | amitriptyline, amitriptyline-chlordiazepoxide, amitriptyline-perphenazine, desipramine, imipramine, nortriptyline, duloxetine, venlafaxine, milnacipran |

Facility and resident characteristics

Facility characteristics explain variation in whether and how opioid and combination opioid-pain-adjuvant therapies are prescribed.[5,52,56–58] Using ltcfocus data,

we included variables that described the served resident population, occupancy, size, ownership, special care units, and staffing (Table 3).[45]

Age, sex, race, and original reason for Medicare entitlement (OREC) associated with each LTC stay were pulled from the annual CCW Master Beneficiary File corresponding to the start of follow-up in the study. Resident age was grouped into 5-year increments (>65, 65 to 74, 75 to 79, 80 to 84, 85 to 89, and > 90 years of age). Race was grouped into 3 categories: white, black, and other. The three categories for OREC were grouped to create two categories: disability (end-stage renal disease and disability) and age.

Available comorbidities that could affect an individual's ability to express pain or might predispose residents to pain treatment were identified from MDS assessments during the study period. If at any time during the LTC stay residents were reported as actively suffering from stroke, depression, schizophrenia, or brain injury, the stay was flagged as being associated with that diagnosis.

*Table 3: Facility characteristics identified from ltc.org database.* [45]

| Category | Variable | Variable definition |
|---|---|---|
| Resident population | Proportion of LTC residents with daily pain | Percentage of long-stay residents during the second quarter of the year with self-report of daily pain. |
| | Proportion of residents with pressure ulcers | Percentage of high-risk long-stay residents with a pressure ulcer. |
| | Proportion of residents with restraints | The number at the time of the annual survey of facility residents who were restrained divided by the total number of facility residents. |
| | Proportion of residents with schizophrenia or bipolar disorder | The proportion of the facility population on the 1st Thursday in April with the most recent MDS assessment reporting schizophrenia or bipolar disorder as a diagnosis. |

*Table 3 continued. Facility characteristics identified from ltc.org database.* [45]

| | | |
|---|---|---|
| | Proportion of residents with Medicaid as primary payer | Proportion of facility population with Medicaid as primary payer at the time of the annual survey. |
| | Proportion of residents with Medicare as primary payer | Proportion of facility population with Medicare as primary payer at the time of the annual survey. |
| | Proportion of nursing home days used for skilled nursing services | Proportion of all nursing home days during the calendar year that were skilled nursing facility Medicare covered days. |
| | Average acuity index | Acuity index is the average measure of need by a nursing home's population. It is calculated based on resident's activities of daily living assistance and receipt of special treatments. |
| Occupancy and size | Occupancy rate | The number of occupied beds divided by the total beds in a facility |
| | Total beds | The number of Medicare or Medicaid certified beds in a facility |
| Ownership | For profit | Whether a facility if for profit |
| | Hospital based | Whether a facility is affiliated with a hospital |
| | Part of a chain | Whether a facility is part of a chain |
| Special care unit | Any special care unit | Whether a facility has any special care unit |
| | Alzheimer's special care unit | Whether a facility has an Alzheimer's special care unit |
| Hospitalization rate | Hospitalization rate | |
| Staffing | Certified nursing assistant (CNA) rate | CNA hours per resident per day |
| | Licensed practical nurse (LPN) rate | LPN hours per resident per day |
| | Registered nurse (RN) rate | RN hours per resident per day |
| | Direct staff rate | Other staff hours per resident per day |
| | Nurse ratio | Proportion of nursing staff that are RNs |

Statistical analysis

Bivariate analysis was used to compare resident and facility characteristics among stays with and without opioid use. Depending on data structure, we used student t-tests, Mann-Whitney U tests, and chi-squared tests to compare differences. Cochran-Armitage

Trend Test was used to identify significant 2011 to 2015 changes in unadjusted annual trends in proportions of opioid-pain adjuvant combination use, any opioid use, chronic opioid therapy, high dose opioid therapy, and opioid saturation ≥50% stay-year days. P-values less than 0.05 were considered significant.

To summarize annual trends in opioid use accounting for variations in facilities and facility populations, logistic regression models with generalized estimating equations (GEE) with sandwich estimators and fixed-year effects were used. One resident could provide multiple stays and one stay could span across multiple years. Generalized estimating equations with sandwich estimators account for clustering at the beneficiary- and stay-level and provide robust maximum likelihood variance estimates even if the model is mispecified.[59] Clustering at the facility-level was rarely found and thus not accounted for in our GEE model. All analyses were conducted at the stay-year level. Models were run among all LTC stays and among stays associated with cancer, CNNP, dementia, and hospice.

## Results

### LTC stay characteristics

We identified 122,970 LTC stays among 83,005 unique Medicare beneficiaries which produced 244,343 stay-years occurring during 2011 to 2015. The average number of stays per resident was 1.5 (SD=0.84); 32.4% of residents had more than one stay. Cancer, dementia, and NCCP were present in 9.1%, 55.3%, and 79.9% of LTC stays, respectively. Hospice stays accounted for 16.9% of LTC stays.

Opioid use was found in 63,316 (50.5%) of stays. Compared to stays without opioid use, residents with opioid-related stays were more likely to be younger, white, and

have disability as their original reason for Medicare eligibility (Table 4). Relative to stays associated with no opioid use, opioid-related stays were longer (median stay = 457 Vs. 386 days, p<0.0001).

Compared to stays without opioid use, chain and hospital-based facility use were more frequent (50.1 vs. 55.3%, p< 0.0001 and 3.5% vs. 3.0%, p=0.0069) in opioid-related stays. Opioid-related stays also were associated with facilities with lower occupancy rates and greater average staff time spent with residents (Table 4). Pain-adjuvant medication use was more common in stays with any opioid use. The most common pain adjuvants used during opioid-related stays were AC (27.6%) and MR (14.2%) and AD (16.0%). No claims for triptan medications during the study period were found (Table 4).

*Table 4: Select resident and facility characteristics among LTC Medicare beneficiary stays who did and did not receive opioid therapy, 2011 to 2015.*

| | No opioid use | | Opioid use | | |
|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ |
| Total stays | 59654 | 47.6% | 63316 | 50.5% | |
| *Resident demographics* | | | | | |
| Age-group | | | | | |
| >65 | 6216 | 10.4% | 6994 | 11.0% | <0.0001 |
| 65-74 | 8458 | 14.2% | 9959 | 15.7% | |
| 75-79 | 6817 | 11.4% | 7506 | 11.9% | |
| 80-84 | 9744 | 16.3% | 10522 | 16.6% | |
| 85-89 | 12578 | 21.1% | 12873 | 20.3% | |
| 90+ | 15841 | 26.6% | 15462 | 24.4% | |
| Female sex | 40684 | 68.2% | 47448 | 74.9% | <0.0001 |
| race | | | | | |
| white | 46985 | 78.8% | 53568 | 84.6% | <0.0001 |
| black | 8986 | 15.1% | 7272 | 11.5% | |
| other | 3546 | 5.9% | 2345 | 3.7% | |
| missing | 137 | 0.2% | 131 | 0.2% | |

Table 4 continued: Select resident and facility characteristics among LTC Medicare beneficiary stays who did and did not receive opioid therapy, 2011 to 2015.

| | | | | | |
|---|---|---|---|---|---|
| OREC | | | | | |
| age | 44179 | 74.1% | 44667 | 70.5% | <0.0001 |
| disability | 15475 | 25.9% | 18649 | 29.5% | |
| Associated diagnoses | | | | | |
| stroke | 13249 | 22.2% | 14004 | 22.1% | 0.6975 |
| depression | 33494 | 56.1% | 42240 | 66.7% | <0.0001 |
| schizophrenia | 5732 | 9.6% | 3741 | 5.9% | <0.0001 |
| brain injury | 786 | 1.3% | 670 | 1.1% | <0.0001 |
| Combination opioid therapy with | | | | | |
| triptans | 0 | | 0 | | |
| AD | 4,297 | 7.2% | 10,113 | 16.0% | <0.0001 |
| steroid | 3418 | 5.7% | 6481 | 10.2% | <0.0001 |
| MR | 3783 | 6.3% | 9048 | 14.3% | <0.0001 |
| AC | 7481 | 12.5% | 17514 | 27.7% | <0.0001 |
| | | | | | |
| *Facility characteristics* | | | | | |
| Hospital based | 1817 | 3.0% | 2203 | 3.5% | <0.0001 |
| Any special care unit | 13234 | 22.2% | 14188 | 22.4% | 0.3464 |
| Alzheimer's special care unit | 11947 | 20.0% | 12927 | 20.4% | 0.0893 |
| for profit | 42561 | 71.3% | 45326 | 71.6% | 0.3505 |
| % in a chain | 29876 | 50.1% | 35023 | 55.3% | <0.0001 |
| | | | | | |
| | mean(SD) | median | mean(SD) | median | p-value |
| Occupied beds/total number of beds[a] | 85.2(12.6) | 88.9 | 84.4(12.7) | 88 | <0.0001 |
| Proportion in restraints[a] | 2.5(5.0) | 0.9 | 2.5(5.0) | 0.9 | 0.1026 |
| Primary payer[a] | | | | | |
| Medicaid | 65.6(18.4) | 68.4 | 64.4 (17.2) | 66.7 | <0.0001 |
| Medicare | 13.4 (9.8) | 11.7 | 13.7 (9.5) | 12.2 | <0.0001 |
| average acuity index[b] | 12.1(1.6) | 12.2 | 12.1(1.5) | 12.2 | <0.0001 |
| staffing[b] | | | | | |
| CNA hours per resident day | 2.3(0.6) | 2.3 | 2.3(0.6) | 2.3 | 0.0955 |
| LPN hours per resident day | 0.8(0.4) | 0.8 | 0.8(0.4) | 0.8 | <0.0001 |
| RN hours per resident day | 0.4(0.3) | 0.4 | 0.4(0.3) | 0.3 | <0.0001 |
| direct staff hours per resident day | 3.5(0.8) | 3.5 | 3.8(0.8) | 3.7 | <0.0001 |

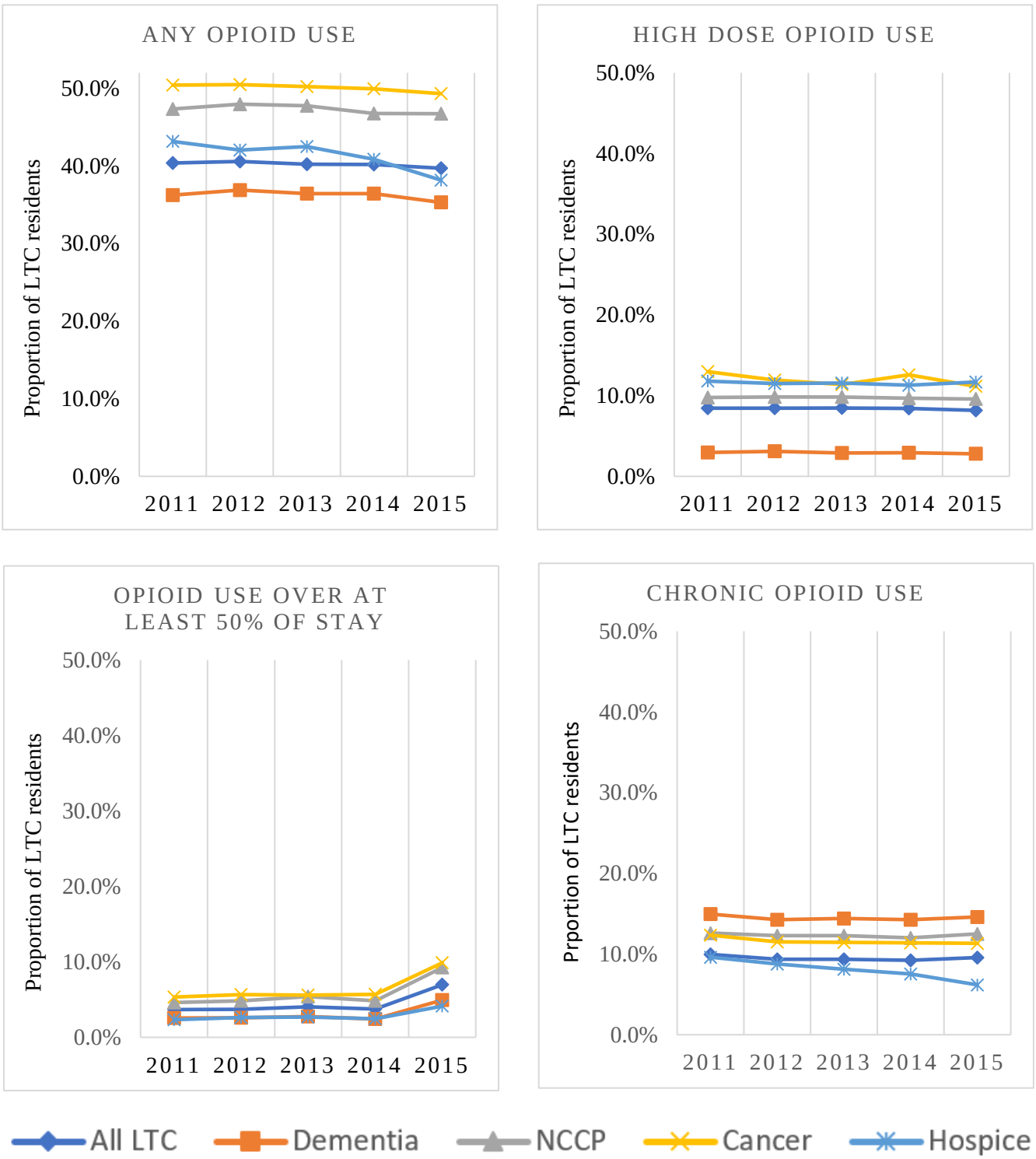
Trends in opioid and opioid-adjuvant combinations

Trends in opioid use are shown in Figure 3. From 2011 to 2015, we found a small but steady decline in opioid use from 40.4% in 2011 to 39.7% in 2015 (p=0.0129). Except for cancer stays, similar declines over the study period were seen in dementia (36.2% to 35.3%, p=0.0304), NCCP (47.4% to 46.7%, p=0.0104) and hospice (43.2% to 38.2%, p<0.0001) stays. From 2011 to 2015, significant changes in high-dose opioid therapy was only found in the cancer stays (13.0% to 11.1%, p=0.0296). Only hospice stays experienced a significant change in chronic opioid use from 2011 to 2015 (9.6% to 6.2%, p<0.0001). Over the study period from 2011-2015, we found significant increases in the proportion of LTC stays with opioid use over at least half of the stay in the general (3.7% to 7.0%, p<0.0001), dementia (2.5% to 4.9%, p<0.0001), NCCP(4.6% to 9.8%, p<0.0001), cancer (2.3% to 4.1%, p<0.0001), and hospice (2.3% to 4.1%, p<0.0001) stays.

Changes in use of pain-adjuvant medications in combination with opioid therapy varied across studied medication classes and subpopulations (Figure 4). AD and opioid combinations increased significantly in general (2.6% to 2.7%, p=0.0003), dementia (4.4% to 4.7%, p=0.0114), NCCP (7.2% to 7.9%, p=0.0011), and cancer (6.2% to 7.9%, p=0.0100) but not in hospice stays (6.9% to 7.9%, p=0.2869). Steroid use in combination with opioids changed significantly from 2011 to 2015 in only hospice stays (2.5% to 1.9%, p=0.015). Use of MR- opioid combinations increased significantly across all subpopulation-stays tested (p<0.0001 for all). Increases of 3.0%, 2.3%, 3.6%, 3.6% and 2.4% from 2011 to 2015 were found in the general, dementia, NCCP, cancer, and hospice LTC stays. Significant changes in AC-opioid combinations also were found. From 2011

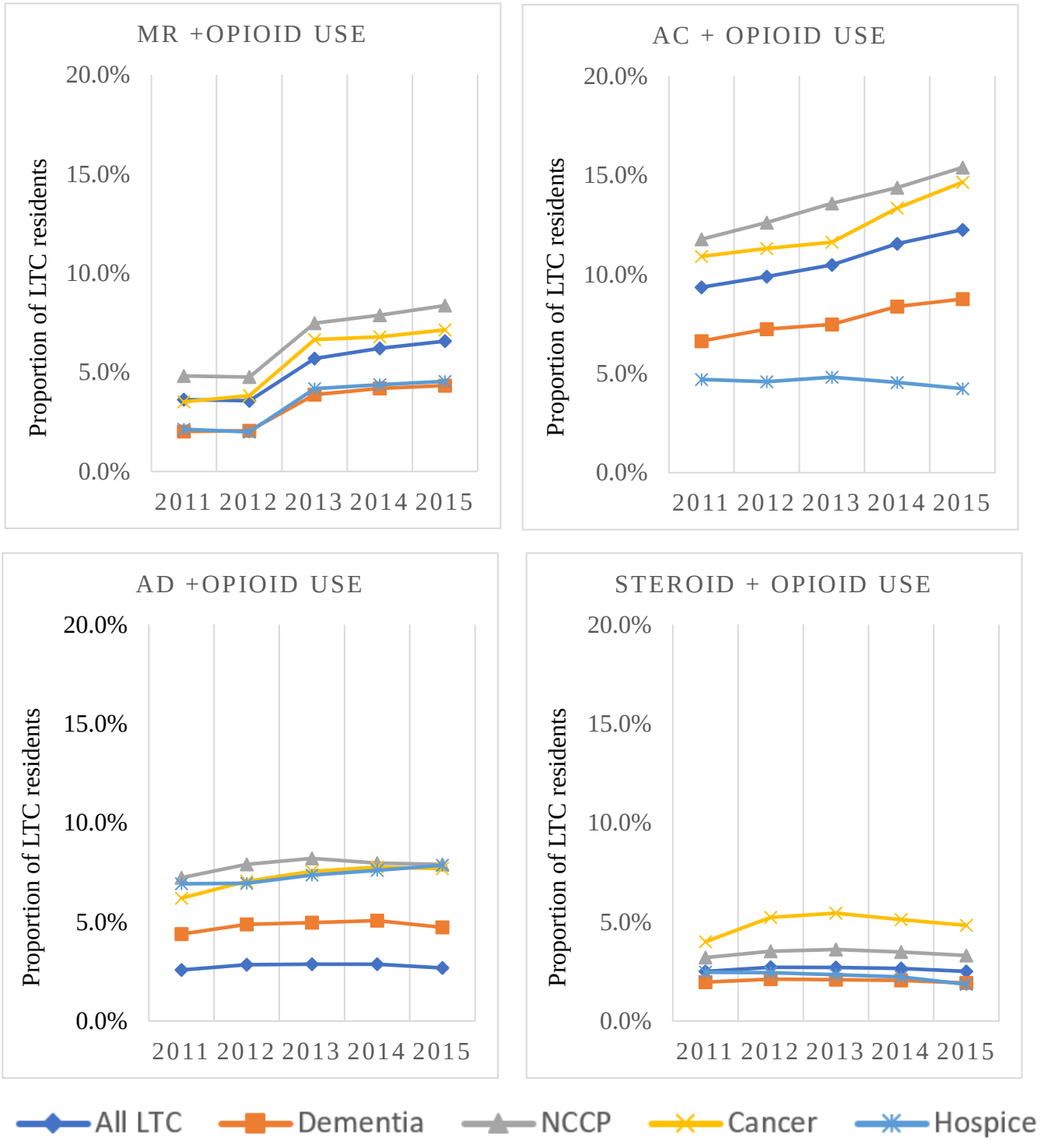
to 2015 we found significant (all p <0.0001) increases of 2.9%, 2.1%, 3.6%, and 3.7% in the general, dementia, NCCP, and Cancer LTC stays, respectively. A decrease in AC-opioid combination use was found among hospice LTC stays (4.7% to 4.2%, p=0.0072). Analyses of pain-adjuvant medications alone also noted increased use over the study period (data available from author).

*Figure 3: Tends in opioid use by subpopulation in long-term care.*




1. Cochran-Armitage Trend Test identified significant 2011 to 2015 changes. For chronic opioid use, only hospice had $p<0.05$. For any opioid use, all cohort differences had $p<0.05$ except cancer for high dose opioid use. Only cancer had a $p<0.05$ for opioid use at least 50% of stay.

*Figure 4: Trends in opioid pain-adjuvant combination use by subpopulation in long-term care nursing home residents.*[1]




1.Cochran-Armitage Trend Test identified significant 2011 to 2015 changes. For MR+opioid and AC+opioid use, all cohorts had $p<0.05$. Steroid+opioid use decreased significantly in only hospice cohorts ($p=0.015$). AD+opioid use increased significantly in all but the hospice cohort.

Adjusted analysis findings

Tables v and vi summarizes findings from our adjusted and unadjusted analyses, respectively. Relative to 2011, we did not find consistent significant annual increases in odds of any opioid-only measure among general or subpopulation LTC stays. Relative to 2011, however, we did find consistent and significant increases in the odds of receiving AC + opioid, and MR + opioid combinations across all studied subpopulation stays. Relative to 2011, overall LTC odds of AC-opioid combinations and MR-opioid combinations increased 31% and 81% in 2015. Among hospice populations, the increase in odds of AC-opioid and MR-opioid combinations from 2011 to 2015 were 20% and 126%. Increases in odds of AC-opioid and MR-combinations in NCCP (32% and 75%)Str and cancer (39% and 114%) in LTC stays in 2015 versus 2011 were found. Dementia stays also had increases; relative to 2011, odds of AC-opioid combinations increased by 33% and odds of MR-opioid combinations increased by 116%.

*Table 5: Annual adjusted odds for select patterns of opioid use among the general, Hospice, NCCP, Cancer and Dementia LTC stays.*

| Population | Any opioid use | Chronic opioid use | High dose Opioid use | ≥50% days Opioid use | AD and Opioid use | Steroid + Opioid use | AC and Opioid use | MR and Opioid use |
|---|---|---|---|---|---|---|---|---|
| | aOR | aOR | aOR | aOR | aOR | aOR | aOR | aOR |
| All LTC | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.04 | 1.00 | 1.00 | 1.02 | 1.11[c] | 1.14[c] | 1.08[c] | 1.01 |
| 2013 | 1.02 | 1.06 | 0.96 | 1.08 | 1.09[c] | 1.50[c] | 1.13[c] | 1.64[c] |
| 2014 | 1.01 | 1.00 | 0.92[b] | 0.91[b] | 1.05 | 1.09[a] | 1.22[c] | 1.67[c] |
| 2015 | 0.98 | 1.12 | 0.89[b] | 0.86[c] | 1.04 | 1.05 | 1.31[c] | 1.81[c] |
| Hospice | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref.[d] | Ref.[d] | Ref. | Ref. |
| 2012 | 1.00 | 0.97 | 0.94 | 1.14 | 1.01 | 1.03 | 1.03 | 0.95 |
| 2013 | 1.04 | 1.08 | 0.94 | 1.16 | 1.09 | 1.00 | 1.10 | 2.08[c] |
| 2014 | 0.95 | 0.90[a] | 0.94 | 1.02 | 1.00 | 0.93 | 1.10 | 2.03[c] |
| 2015 | 0.89[b] | 0.98 | 0.98 | 1.81 | 0.98 | 0.81 | 1.20[c] | 2.26[c] |

*Table 5 continued: Annual adjusted odds for select patterns of opioid use among the general, Hospice, NCCP, Cancer and Dementia LTC stays.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cancer | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 0.99 | 0.92 | 0.88 | 1.02 | 1.12 | 1.35[b] | 1.03 | 1.11 |
| 2013 | 0.98 | 0.96 | 0.75[c] | 0.99 | 1.19 | 1.42[b] | 1.04 | 1.99[c] |
| 2014 | 0.95 | 0.90 | 0.81 | 0.98 | 1.17 | 1.30[a] | 1.19[a] | 1.95[c] |
| 2015 | 0.95 | 1.06 | 0.75[b] | 1.80[c] | 1.21 | 1.27 | 1.39[c] | 2.14[c] |
| NCCP | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.03[a] | 1.01 | 1.02 | 1.03 | 1.10[c] | 1.13[b] | 1.08[c] | 0.99 |
| 2013 | 1.03 | 1.08[c] | 0.99 | 1.14[c] | 1.12[c] | 1.18[c] | 1.15[c] | 1.59[c] |
| 2014 | 0.99 | 1.03 | 0.94 | 0.99 | 1.06[a] | 1.12[c] | 1.21[c] | 1.61[c] |
| 2015 | 0.99 | 1.16[c] | 0.93 | 2.04[c] | 1.05 | 1.09 | 1.32[c] | 1.75[c] |
| Dementia | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.06 | 1.01 | 1.03 | 1.03 | 1.13[c] | 1.13[a] | 1.12[c] | 1.04 |
| 2013 | 1.05 | 1.07[c] | 0.95 | 1.10 | 1.15[c] | 1.14[a] | 1.15[c] | 2.00[c] |
| 2014 | 1.03 | 1.02 | 0.96 | 0.93 | 1.12[c] | 1.09 | 1.25[c] | 2.03[c] |
| 2015 | 0.99 | 1.07[c] | 0.92 | 1.96[c] | 1.01 | 1.06 | 1.33[c] | 2.16[c] |

a. Odds ratios with significant values $p<0.05$.
b. Odds ratios with significant values $p<0.01$.
c. Odds ratios with significant values $p<0.001$.
d. Sample size was too small to run full model. Odds ratios reported are from model controlling for only race, sex, age and clustering at the individuals and stay-level.

*Table 6: Annual unadjusted odds for select patterns of opioid use among the general, Hospice, NCCP, Cancer and Dementia LTC stays.*

| Population | Any opioid use | Chronic opioid use | High-dose Opioid use | ≥50% days Opioid use | AD and Opioid use | Steroid + Opioid use | AC and Opioid use | MR and Opioid use |
|---|---|---|---|---|---|---|---|---|
| | OR | OR | OR | OR | OR | OR | OR | OR |
| All LTC | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.01 | 0.92[b] | 1.03 | 1.02 | 1.09[b] | 1.08[a] | 1.06[b] | 0.94 |
| 2013 | 0.99 | 0.94[b] | 1.00 | 1.10[a] | 1.10[b] | 1.08[a] | 1.13[b] | 2.01[b] |
| 2014 | 0.99 | 0.92[b] | 0.99 | 1.02 | 1.11[b] | 1.06 | 1.26[b] | 2.11[b] |
| 2015 | 0.97[a] | 0.98 | 0.96 | 1.96[b] | 1.10[b] | 1.00 | 1.35[b] | 2.19[b] |
| Hospice | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 0.96 | 0.88[b] | 0.96 | 1.13 | 0.97 | 0.99 | 1.00 | 0.94 |
| 2013 | 0.97 | 0.89[b] | 0.97 | 1.15 | 1.03 | 0.95 | 1.07 | 2.01[b] |
| 2014 | 0.91[b] | 0.78[b] | 0.99 | 1.06 | 0.97 | 0.90 | 1.11 | 2.11[b] |
| 2015 | 0.81[b] | 0.70[b] | 1.06 | 1.80[b] | 0.90 | 0.75[a] | 1.15[a] | 2.20[b] |

*Table 6 continued: Annual unadjusted odds for select patterns of opioid use among the general, Hospice, NCCP, Cancer and Dementia LTC stays.*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cancer | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.00 | 0.90 | 0.91 | 1.06 | 1.15 | 1.33 [a] | 1.04 | 1.09 |
| 2013 | 0.99 | 0.91 | 0.78 [a] | 1.05 | 1.24 [a] | 1.40 [b] | 1.07 | 1.96 [b] |
| 2014 | 0.98 | 0.86 [a] | 0.88 | 1.08 | 1.27 [a] | 1.30 [a] | 1.26 [b] | 2.00 [b] |
| 2015 | 0.96 | 0.93 | 0.79 [a] | 1.96 [b] | 1.26 [a] | 1.22 | 1.40 [b] | 2.11 [b] |
| NCCP | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.02 | 0.98 | 1.03 | 1.05 | 1.10 [b] | 1.10 [a] | 1.08 [b] | 0.98 |
| 2013 | 1.02 | 1.00 | 1.03 | 1.18 [b] | 1.15 [b] | 1.13 [b] | 1.18 [b] | 1.60 [b] |
| 2014 | 0.98 | 0.96 [a] | 1.00 | 1.05 | 1.11 [b] | 1.09 [a] | 1.26 [b] | 1.70 [b] |
| 2015 | 0.98 | 1.03 | 0.99 | 2.11 [b] | 1.10 [b] | 1.03 | 1.36 [b] | 1.80 [b] |
| Dementia | | | | | | | | |
| 2011 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 2012 | 1.03 | 0.95 [a] | 1.05 | 1.02 | 1.12 [b] | 1.08 | 1.10 [b] | 1.20 |
| 2013 | 1.01 | 0.96 [a] | 0.98 | 1.09 | 1.14 [b] | 1.07 | 1.14 [b] | 1.96 [b] |
| 2014 | 1.01 | 0.95 [a] | 0.99 | 0.95 | 1.16 [b] | 1.05 | 1.29 [b] | 2.13 [b] |
| 2015 | 0.96 [a] | 0.97 | 0.95 | 2.00 [b] | 1.08 | 0.98 | 1.35 [b] | 2.20 [b] |

a. Odds ratios with significant values $p<0.05$.
b. Odds ratio with significant values $p<0.01$.

## Discussion

Despite concerns regarding the opioid epidemic in the general U.S. population, adjusted analyses did not indicate constant or statistically significant changes in dose, duration, or frequency of opioid use from 2011 to 2015 in LTC populations. Opioids and opioid-pain-adjuvant combinations were used differently across our study subpopulations; any opioid use was most common in cancer-related stays and less common in hospice and dementia-related stays. Adjusted analyses did find statistically significant and constant increases in stays involving opioid use with anticonvulsants or skeletal muscle relaxants overall and in all subpopulations. There are several possible reasons for this seen increase. One is that LTC providers challenged with limited medications to address multifaceted pain etiologies are using low-dose multimodal treatment approaches to avoid safety-effects, such as sedation-related falls, from high

dose opioid therapy.[60] Another could be that policies in response to rising rates of opioid overdose in the general population, may have led prescribers to favor use of add-on pain-adjuvant therapy (specifically, anticonvulsant, skeletal muscle relaxant, and antidepressant pain adjuvants) over increasing opioid doses.

Use of opioids and opioid-pain adjuvant combinations did vary across the subpopulations studied. Any opioid use, high-dose opioid use, and opioid saturation ≥50% were most common among LTC stays associated with cancer. Consistent with previous literature, individuals reported as having an active diagnosis of dementia were least likely to receive any or high dose opioid therapy.[17] We were surprised to find that the proportion of LTC stays with ≥50% opioid use saturation was similar among dementia and hospice populations. This may suggest similar inabilities to effectively identify pain among residents at end-of-life and with dementia might be leading to inadequate pain treatment. Opioid combinations with ADs, MRs and ACs were most frequently found in stays associated with NCCP. Combination opioid-steroid combinations were most frequently found in LTC stays associated with cancer.

Changes in combination adjuvant pain medications and opioid use also varied among our studied subpopulations. Among those studied, the largest increase in odds from 2011 to 2015 in opioid combinations with MRs and ACs were seen in the dementia and cancer subpopulations. Given the reports of undertreatment and guideline recommendations for multimodal pain treatment for pain in cancer, this increase in cancer LTC stays is promising.[57,61] Evidence for the added benefit of these combination therapies for pain in individuals with dementia and other subpopulations, however, are less clear. Skeletal muscle relaxants are centrally-active depressants known to negatively

impact cognitive function.[62–65] Also, pain adjuvants with anticholinergic properties, such as MRs and ADs, decrease levels of acetylcholine in the central nervous system. This directly antagonizes cholinesterase inhibitors which slow cognitive and functional decline by increasing central nervous system levels of acetylcholine.[66] Moreover, studies on the additive risks of taking multiple CNS medications in older adults have found increased risks of falls and hospitalizations.[3,43,44] Given this potential drug interaction and the ability for MRs to exacerbate dementia sequalae, further research on the outcomes and benefits of this combination in this LTC population is needed.

This study has several limitations and strengths. Our trend analysis is only from 2011 to 2015, which may be during a uniquely stable period for opioid use. Future studies utilizing longer time frames might support the salience of trends identified in this study. While we did control for all medical conditions available in our MDS dataset, there could be confounding conditions that were not accounted for. As with all Medicare Part D claims-based analyses, we were unable to identify indications for medication use and did not evaluate the use of over-the-counter medications. For Medicare beneficiaries who began hospice services before or at some point during their long-term stay, opioid and pain adjuvant medication use may have been underestimated. Medicare provides a set daily reimbursement rate for individuals receiving hospice that includes medications; thus, use of medication including opioids are not discernable from claims.[67] Other future studies using different data sources could ensure full capture of prescription medications among hospice patients, the indications of adjuvant medications , reducing the likelihood for misclassification of pain adjuvants used for purposes other than pain, and report over-the-counter pain-reliever use. Finally, we relied on a dataset of self-report of dementia

diagnoses which might under-report the presence of this condition. Report of dementia diagnosis on MDS 3.0 might serve as a better indicator of the facilities awareness of a diagnosis.

Our study used multiple data sources to provide facility- and resident characteristic- adjusted national trends in opioid and pain-adjuvant medication use over the entire LTC stay in subpopulations likely to require or be exposed to opioid and adjuvant medications. We are the first known study to describe the use of concurrent opioid and MR medications. We did not exclude cancer and hospice stays; cancer-related and hospice stays accounted for nearly 30% of all LTC stays with opioid use. Analyses of LTC stays that exclude these populations would have lower opioid prevalence estimates. Finally, we also accounted for increased risk of opioid exposure with increasing length of LTC stay by creating an opioid-use saturation measure describing the proportion of days during a stay in which opioids were supplied.

In conclusion, opioid use is common during LTC stays. Combination use of opioids with ACs or MR in the general, cancer, dementia, hospice, and NCCP LTC populations increased between 2011 and 2015. We do not know the clinical implications of this increase. Research on the risks of falls, sedation, cognitive decline, and overdose associated with opioid combinations are needed to help prescribers, residents, and policy makers ensure quality pain treatment.

**Aim 2: Changes in Opioid Dose Over Time Among Long-Term Care Nursing Home residents: A Latent Class Growth Modeling Analysis.**

Abstract

Background: Analgesic tolerance, disease progression, and acute illness episodes are frequent in nursing home residents and could lead to opioid dosing changes. These changes could affect safety-related risks. No known study has identified different dosing patterns over time in this setting.

Objectives: Identify common opioid dose patterns among long-term care (LTC) nursing home Medicare beneficiaries over 180 days and assess associations with opioid-related resident characteristics.

Methods: This 2011-2015 cross-sectional study included 12,605 LTC residents receiving opioid therapy from a 5% national sample of Medicare beneficiaries. Latent class growth modeling (LCGM) identified patterns of average morphine equivalent daily dose (MEDD) across six 30-day intervals starting with the first opioid prescription dispensed in the nursing home. Multinomial multivariate regression quantified associations between different opioid use patterns over time and clinical and demographic resident characteristics.

Results: The most common opioid dosing pattern identified was extended high (49.9%), followed by short-term (27.1%), intermittent (14.7%) and restart (8.3%). Associations with receipt of extended high therapy, or 90 average MEDD over 180-days, and prior opioid use (aOR[95%CI]=4.41[3.79-5.15]), antidepressants (aOR[95%CI]=1.34[1.15-1.55]), skeletal muscle relaxants (aOR[95%CI]= 1.18[1.01-1.38]), steroids(aOR[95%CI]=1.27[1.02-1.57]), and non-pharmacological pain

treatments(aOR[95%CI]=1.73[1.56-1.91]) were found. Associations with race, female sex, intact cognition and select psychiatric disorders were also identified.

Conclusion: LTC Medicare beneficiaries experience four different opioid dosing patterns. Residents receiving different dosing patterns varied in demographic and clinical resident characteristics. More research is needed to evaluate how varying opioid dosing strategies over time are associated with health-related outcomes in LTC residents.

## Introduction

Annually, 794,000 people in the United States will reside in a nursing home for more than 100 days.[9] An estimated 38.6% of these long-term care (LTC) residents have pain; half of LTC residents with pain have persistent pain or pain lasting longer than 3 months.[36] Lack of practical alternatives make opioid therapy a common treatment choice, with one in three residents receiving opioid therapy in the first 120 days of their stay.[3,36,52] Opioid use is not without risks, as these often older, frail, and multimorbid residents are particularly vulnerable to opioid-related sedation, falls, and respiratory depression.[1,40]

Progression of disease and episodes of acute illness are common among nursing home residents and could lead to frequent changes in opioid therapy.[68] Different opioid dose rate and magnitude changes could result in different opioid-related safety risks.[68] Studies evaluating the outcomes associated with different patterns of opioid dose over time are sparce. One small study of 66 nursing home residents found that opioid treatment interruptions, defined as dose reductions as greater than 50% for at least one day, were common and associated with worse pain.[68] Other studies outside of the nursing home population have shown no increased analgesic benefit with opioid dose escalations, and increased pain-related problems (e.g., worse pain, sleep difficulty, behavioral

problems) with treatment cessation in chronic non-cancer pain patients.[68–72] No known study describes how and in whom opioid dose changes over time in the nursing home setting.

Latent class growth modeling (LCGM) is a semi-parametric technique that identifies distinct subgroups of individuals following similar patterns of change across multiple time points. Unlike traditional statistical techniques, such as analysis of variance (ANOVA), multiple aggression, multivariate analysis of variance (MANCOVA), and system of equation modeling (SEM), LCGM can identify clusters of individuals where both the strength and direction of change between each time point can vary.[73] LCGM identifies homogenous groups with similar patterns over time allowing for later comparisons across other variables.

Previous studies assessing use and safety-risk of opioid therapy in nursing home populations have not considered different patterns of opioid use over time.[74–77] Given the probability of dosing changes and the potential impact of those changes on patient safety, a complete understanding of how, where, and in whom opioids are prescribed over time are needed. To aid in this understanding, our objective was to identify common opioid dose patterns over time. While we were not sure what the patterns would look like, we hypothesized that we would find identify multiple distinct dosing patterns. We expected that these distinct groups to be highly associated with resident factors already identified in previous literature as associated with receipt of pain treatment and safety-related risks (e.g., cognitive function, use of other medications, psychiatric disorders, and pain-related diagnoses).

## Methods

This cross-sectional study used Medicare Parts A, B, and D claims and the Minimum Dataset 3.0 (MDS) from January 1st, 2011 to December 31st, 2015. Medicare Parts A, B, and D claims provided all fee-for-service institutional and non-institutional claims, enrollment/eligibility information, and prescription opioid use for a nationally representative 5% sample of Medicare beneficiaries. MDS provided quarterly assessments describing active diagnoses, cognitive impairment, behavioral problems, and nursing home stay length. Data were linked using unique Centers for Medicare and Medicaid beneficiary identification codes.

### Study Sample

For our study, we followed all LTC Medicare beneficiaries upon entry into the nursing home or 30 days prior to the first opioid prescription in the nursing home, whichever came first, and then for 180 days following their first opioid prescription fill. The 30-day look back period was longer than the time it would take to develop tolerance (i.e., 3 weeks)[68,78,79] plus the average duration of a hospital stay[80] and allowed for differentiation between prevalent and incident opioid users. Consistent with previous literature, Medicare beneficiaries were identified as LTC residents if the total days between admissions and discharge (or the last available assessment date) after subtracting days associated with SNF services was at least 100 days. [46–48]

Additional inclusion criteria included survival for 180 days after initiating opioid therapy in the nursing home and continuous enrollment in Medicare Parts A, B, and D during the stay and for at least one month prior to the index opioid prescription. Continuous coverage allowed for accurate identification and characterization of LTC

residents and opioid use. Residents with stays associated with hospice care or with Medicare Advantage insurance during the stay were excluded. From our 5% sample, we found 12,617 eligible LTC residents for our study.

Measures

Opioid Therapy

All opioid, opioid combination, and pain-adjuvant products identified in Medicare Part D claims included in our analysis are reported in table 7. Starting with the first opioid prescription dispensing date, we identified the average morphine equivalent daily dose (MEDD) across 6 discrete 30-day intervals. Opioid prescriptions were transformed into MEDD by multiplying the strength per unit in milligrams by the average daily units dispensed and the oral morphine equivalent conversion factor (OME).[54] We capped MEDD at 180 mg/day to prevent individual extreme high-dose prescriptions from inflating our calculations. We chose 180mg/day because it is twice the 90 mg daily dosing cautioned against in the 2016 CDC guidelines on prescribing opioids for chronic pain and three times the threshold for high-dose therapy (50 MEDD) used in literature evaluating nursing home residents.[1,16] To calculate average MEDD per interval, we summed all MEDDs per interval then divided by the number of interval days that resident received opioid therapy (Equation 1).

*Equation 1: Equation for calculating average MEDD per interval from Medicare part D claims.*

$$\frac{\sum((\frac{strength(mg)}{unit}) * (\frac{units\ dispensed}{days'supply}) * interval\ days * OME\ conversion\ factor)}{opioid\ days}$$

Here, days' supply refers to the prescription therapy length in days, interval days refers to the prescription treatment days that fall within each interval, and opioid days refers to the total unique number of days across all prescriptions within each interval that opioids were supplied. All day values were based on prescription dispensing dates and days' supply. While calculating days' supply and opioid days, we assumed overlapping prescriptions of ≥ 1 day were used simultaneously.

Part D claims also provided opioid formulation, route of administration, and whether the opioid therapy was new or prevalent. Opioids identified in the data included tramadol, oxycodone, morphine, fentanyl, hydrocodone, codeine and other (tapentadol, pentazocine, oxymorphone, meperidine, methadone, hydromorphone, levorphanol, butorphanol) formulations. Routes of administration categories included oral, topical, transdermal, sublingual, and parenteral. Residents with opioid use 31 days prior to the first opioid prescription seen in the nursing home were flagged as prevalent opioid users.

*Table 7: Opioid and non-opioid pain adjuvant medications searched for in Medicare part D claims.* [6,55]

| Category | Generic drugs included |
|---|---|
| Opioids and opioid combination products | albuphine, buprenorphine, buprenorphine combination products, codeine, codeine combination products, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, oxycodone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxymorphone, pentazocine, tapentadol, tramadol and opioid combination products |
| Skeletal Muscle Relaxants (SMR) | baclofen, carisoprodol, chlorzoxazone, clonazepam, cyclobenzaprine, metaxalone, tizanidine |
| Anticonvulsants (AC) | carbamazepine, gabapentin, pregabalin, lamotrigine |
| Systemic corticosteroids | betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone |
| Antidepressants (AD) | amitriptyline, amitriptyline-chlordiazepoxide, amitriptyline-perphenazine, desipramine, imipramine, nortriptyline, duloxetine, venlafaxine, milnacipran |

Other pain treatments

To provide a general description of pain treatment among residents in our study, we determined whether residents received only scheduled pain therapy, only PRN (or as needed) pain therapy, scheduled with PRN pain therapy, non-pharmacological pain treatments, or other prescription pain adjuvant medications from MDS assessments and Medicare Part D claims. If any MDS assessment during the 180-day follow-up noted resident receipt of scheduled, PRN, or non-pharmacological pain treatment, those residents were flagged as receiving that therapy (MDS variables J0100A, J0100B, and J0100C). We defined use of skeletal muscle relaxants, anticonvulsants, systemic corticosteroids, or antidepressants often used for pain (Supplement Table 1) as receipt of at least one Part D claim prescription for that agent during follow-up.

Resident characteristics

Several residential characteristics that could explain variations in opioid dosing were evaluated in our study. Age, sex, race, U.S. geographical region, and original reason for Medicare entitlement (OREC) associated with each LTC beneficiary were pulled from the annual CCW Master Beneficiary File corresponding to the start of follow-up in the study. Resident age was grouped into 10-year increments (<65, 65 to 74, 75 to 84, and >85 years of age and older). Race was based on a modified race variable that classified additional beneficiaries as Hispanic or Asian race based on their first or last name.[14] Race was grouped into four categories: non-Hispanic White, non-Hispanic

Black, Hispanic and other. The three categories for OREC were grouped to create two categories: disability (end stage renal disease and disability) and age.

Average cognitive ability was calculated by averaging all available Brief Inventory Mental Status Scores (BIMS) or Cognitive Performance Scales (CPS) available from assessments during the 180-day exposure period. BIMS is a resident-reported measure of cognition that categorizes individuals as cognitively intact (score =13-15), moderately impaired (score=8-12), or severely impaired (0-7).[81,82] Some residents, namely those with cognitive impairment, might not have been able to participate in a BIMS assessment. Among those residents with no available BIMS assessments, an average of the CPS, a staff-reported measure of resident cognition, was used to categorize residents as cognitively intact (score =0-2), moderately impaired (score=2-4) or severely impaired (score=5-6).[83]

Pain-related clinical diagnoses, report of pain, and evidence of persistent pain were identified from both claims and MDS assessments during the 180-day exposure period. Residents flagged as having reported pain had any self or staff report of pain on any assessment during the study period. We defined persistent pain as two or more reports of pain on assessments at least 90 days apart.[84] Active diagnosis flags from the MDS identified pain-related comorbidities (arthritis, osteoporosis, stroke, fracture, pressure ulcers, psychiatric or mood disorders, surgical wounds). Non-cancer chronic pain (NCCP) diagnoses were grouped into seven categories and identified using ICD-9-CM and ICD-10-CM diagnostic codes over the follow-up period (Table 8).

MDS assessments identified delirium, behavioral problems (i.e., verbal behavior, physical behavior, wandering, resistance to care), falls, constipation, pain affecting sleep,

and pain affecting activity. Delirium was identified using the confusion assessment method (CAM) diagnostic algorithm.[85,86]

*Table 8:ICD-9CM and ICD10-CM codes used to define chronic painful conditions from outpatients, skilled nursing and physician claims.* [50–52]

| Painful conditions | ICD- 9 CM Definition | ICD-10 CM Definition |
|---|---|---|
| Chronic pain | 338.0, 338.2x, 338.4 | G89.0, G89.2x, G89.4 |
| Abdominal pain | 533.4x-533.9x, 550.x-553.x, 555.x, 556.x (except 556.4), 564.1, 569.42, 577.1x, 590.0x, 789.0x | K27.4-K27.9, K40.x-K46.x, K50.x, K51.x (except K51.4x), K58.x, K62.89, K86.0, K86.1, N11.x, R10.1x-R10.8 |
| Musculoskeletal pain | | |
| Back/neck pain | 720.x-724.x | M45.x-M55.x |
| Head | 307.81, 339.x, 346.x | G43.x, G44.x |
| Limb pain | 354.4, 355.71, 729.5 | G56.4x, G57.7x, M79.6x |
| Arthritis/rheumatism/ joint pain/myalgia | 274.x, 710.xx-719.xx, 725.x-729.x (excluding 729.5 and 729.2) | M1A.x, M05.x-M08.x, M11.x-M19.x, M22.x-M25.x, M65.x-M67.x, M70.x-M71.x, M75.x-M77.x, M79.x (except 79.6x and M79.2), M94.x |
| Neuropathic pain | 53.1x, 249.6x, 250.6x, 337.1, 337.2x, 340.x, 341.9, 350.x, 351.x, 353.x-356.x, 357.81, 729.2, 951.4, 952.x, 953.x | B02.23, E08.4x, G99.0, G90.5x, G35.x, G37.9, G50.x, G54.x, G56.x(except G56.4), G54.x-G58.x (except G57.7x), G61.81, M79.2, S04.50XA, S14.x, S24.x, S34.x |

Statistical analysis

Latent class growth modeling was used to identify classes of initial opioid dose growth trajectories. Traditional latent growth modeling or mixed growth modeling assume that individuals come from a single population and that a single growth trajectory can adequately represent an entire population. In contrast, LCGM is a person-centered approach, and the goal is to classify individuals into distinct groups or categories based

on individual growth patterns so that individuals within a group are more similar than individuals between groups. In the Latent class growth analysis (LCGA), all individual growth trajectories within a class are homogeneous, while different classes differ in the growth factors (intercept, slopes) from each other.[87] Models were generated in SAS Studio using the PROC TRAJ procedure.[88] For the model, the time scale included six 30-day periods (30 days was the most common opioid prescription length found in the data) starting with the first opioid prescription dispensed in the nursing home. Our dependent variable, mean MEDD, was log transformed as the MEDD was non-normal distributed (before transformation skewness=16.65, kurtosis=594.50 and after transformation skewness=0.14, kurtosis=-1.73). All residents were required to have continuous coverage for at least 180 days after their first opioid prescription; there were no missing opioid dose data during follow-up.

Consistent with recommendations,[73,88] model fit was done in two stages. First, the optimal number of classes were identified by evaluating three criteria in seven censored models with one to seven fixed quadratic groups: changes in the Bayesian information criterion (BIC), a sufficient average group membership probability (>80%), and a sufficient proportion of patients in each group to permit meaningful analysis (i.e., >5% or n>680). Second, different models with linear, quadratic, or cubic line fit was chosen based on the model with the optimal class and were compared based on BIC. The model with the lowest BIC was selected as the best model. As a sensitivity analysis, we also identified trajectories in two restricted cohorts; one cohort was limited to those with at least one seven-day opioid prescription during their follow-up period and another

included only LTC residents who did not have opioid use in the month prior to their first observed opioid prescription in the nursing home.

Residents were assigned to groups in which they had the highest probability of belonging. Mean, standard deviation (SD), and median MEDD among residents in each trajectory groups were calculated for each time interval. Chi-squared statistics were used to compare the proportion of residents in each group who received only scheduled pain medication, only PRN pain medications, both scheduled and PRN pain medications, nonpharmacological pain treatment, opioid therapy prior to entering the nursing home, specific opioid formulations, and differing opioid routes of administration.

To quantify the association of resident characteristics with assignment to a particular group, a multinomial multivariate regression model was used to calculate the adjusted odds ratio of belonging to each trajectory group. Stepwise model selection was used to select independent variables in our model. A likelihood ratio test with significance less than 0.2 was required for final model inclusion. All statistical analyses were performed using SAS version 9.4.

## Results

### Group based trajectory model

The optimal model identified had four groups with quadratic growth: groups included short-term, intermittent, restart, and extended high dose (Figure 5). Relative to the two- and three- group models, the four-group model yielded the smallest BIC and maintained average membership probabilities above 90% and class sizes over 5% (Table 9). Models with more than four groups had diminishing improvements in BIC, clinically insignificant group populations, or average group probability 95% confidence intervals

that dipped below 70%. Quadratic line fit for all groups identified in the 4-group model resulted in the smallest BIC. For the sensitivity analyses, trajectory models among populations limited to individuals without evidence of exposure to opioid therapy prior to entering the nursing home and among individuals who had at least one seven-day period of continuous opioid exposure yielded similar opioid dose patterns over time; results of sensitivity analyses are available by request from the author. Reported results are based on the overall sample.

The most common opioid dosing pattern identified was extended high (49.6%), followed by short-term (26.9%), intermittent (14.9%), and restart (8.6%). As shown in Figure 5 and Table 10, the short-term group had 9 days of opioid therapy, an average MEDD of 12.3, and no opioid exposure after the first 30-day interval (Table 5). The intermittent group was characterized by 19.5 days of opioid therapy over 150 days with an average MEDD ranging from 9.7 to 63.2. The restart group received 19.7 days of opioid therapy over 180-days. In the restart group, average MEDD decreased from 53.7 to 11.6 across over the first 90-days then increased in average MEDD (from 11.6 to 92.9) over 90 days. On average, the extended high dose group received opioids for 75.6 days over the 180-days. Average MEDD in the extended high dose group varied between 80.7 and 98.0.

*Figure 5: Selected group-based trajectory model of the average MEDD used among LTC Medicare beneficiaries during their first 180 days of opioid therapy in the nursing home.*

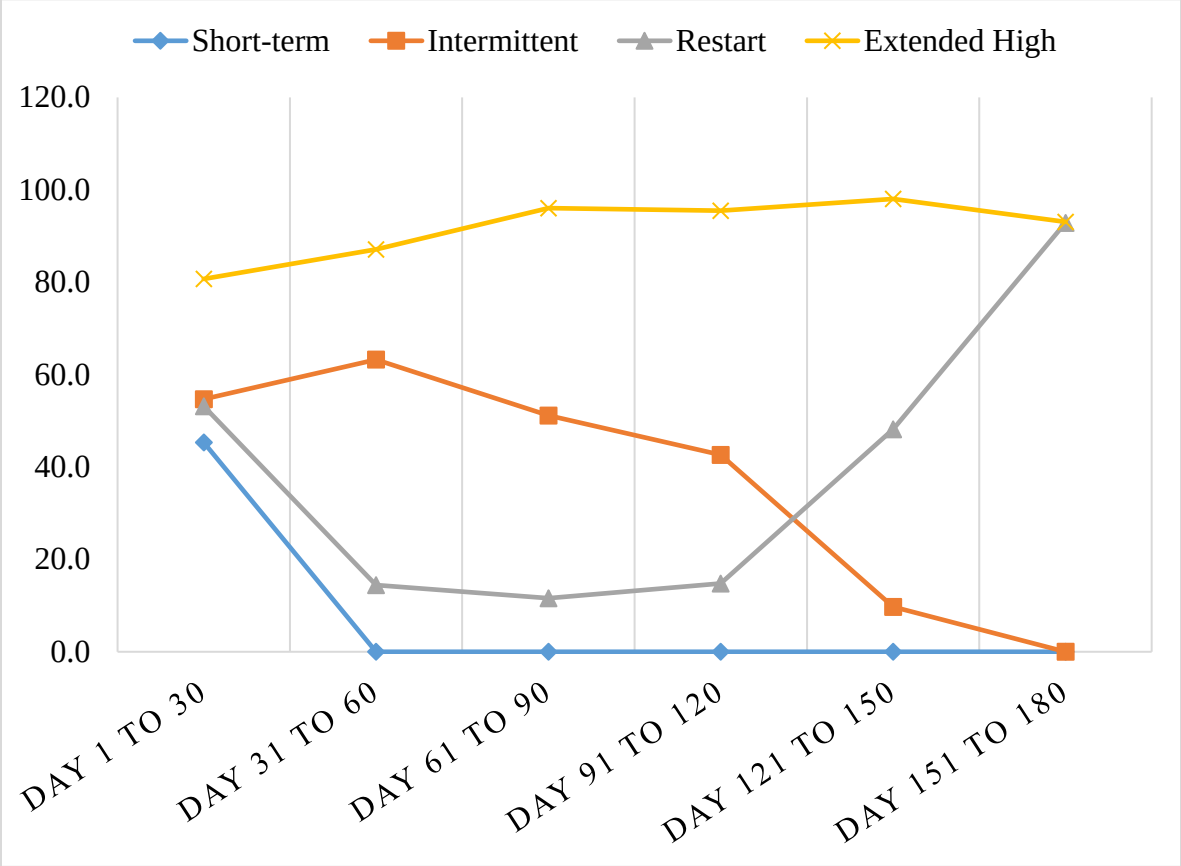



*Table 9: Summary and model fit statistics for 180-day average MEDD trajectory-based models with one to seven groups among LTC Medicare residents.*

| | BIC | Δ | 2*ΔBIC | Lowest average group membership probability, %(SD) | Lowest group proportion (%) |
|---|---|---|---|---|---|
| 1 Class | -143820.5 | -- | -- | 100 | 100 |
| 2 Class | -124396.9 | 19423.6 | 38847.2 | 98.3(6.1) | 42.1 |
| 3 Class | -121234.3 | 3162.5 | 6325.1 | 93.4(12.3) | 23.5 |
| 4 Class | -119503.3 | 1731.1 | 3462.1 | 91.7(10.9) | 8.6 |
| 5 Class | -119525.8 | -22.5 | -44.9 | 91.2(10.9) | 0.0 |
| 6 Class | -118484.6 | 1041.1 | 2082.2 | 72.4(13.2) | 5.9 |
| 7 Class | -118343.3 | 141.3 | 282.6 | 74.0(13.5) | 2.7 |

*Table 10: Mean, standard deviation and median of average morphine equivalent daily dose (MEDD), total days of opioid therapy, and time to opioid therapy initiation among LTC Medicare residents in varying opioid dose trajectory groups over the 180- day follow-up.*

| | Short-term, N=3,416 | Intermittent, N=1,855 | Restart, N=1,044 | Extended high dose, N=6,302 |
|---|---|---|---|---|
| | mean (SD), median | mean (SD), median | mean (SD), median | mean (SD), median |
| Pre-index 30 days | 2.2(12.0), 0.0 | 4.1(15.3), 0.0 | 4.8(19.3), 0.0 | 16.2(38.5), 0.0 |
| 0 to 30 days | 45.3(45.7), 30.0 | 54.7(52.1), 31.3 | 53.7(52.1), 30.0 | 80.7(63.5), 56.1 |
| 31 to 60 days | 0.0(0.0), 0.0 | 63.2(72.9), 20.0 | 14.4(42.7), 0.0 | 87.1(72.1), 73.5 |
| 61 to 90 days | 0.0(0.0), 0.0 | 51.2(70.7), 0.0 | 11.6(39.4), 0.0 | 96.0(71.5), 90.0 |
| 91 to 120 days | 0.0(0.0), 0.0 | 42.6(68.0), 0.0 | 14.8(44.2), 0.0 | 95.5(71.2), 86.7 |
| 121 to 150 days | 0.0(0.0), 0.0 | 9.7(35.3), 0.0 | 48.2(70.5), 0.0 | 98.0(70.8), 95.0 |
| 151 to 180 days | 0.0(0.0), 0.0 | 0.0(0.1), 0.0 | 92.9(75.0), 100.0 | 93.1(71.7), 82.0 |
| | | | | |
| Days of therapy | 8.9(8.0), 12.0 | 19.5(22.4), 10.0 | 19.7(23.5), 10.0 | 73.6(54.6), 68.0 |
| Days to therapy | 151.9(196.1), 84.5 | 110.2(159.9), 58.0 | 115.2(161.1), 64.5 | 75.6(126.9), 40.0 |

Resident characteristics

Comparison of demographic and clinical of residents associated with each MEDD dosing pattern over time are reported in table 11. Sex, age, OREC and geographic region did vary significantly across groups ($p<0.0001$). Compared with other groups, the extended high group had a higher proportion of residents who were female (83.7%), gained Medicare eligibility through disability or ESRD (29.7%), and were Non-Hispanic white (83.7%). The short-term group had the highest proportion of residents over the age of 85 (48.4%) relative to other groups. Residents in the Southern United States were the

most represented across all groups, with the largest proportion seen in the Restart group (40.8%).

Pain and other clinical comorbidities also varied significantly across groups. One in three residents in the extended high group had persistent pain (31.8%). Other groups had a lower prevalence of persistent pain (13.9%-25.1%, in other groups, p<0.0001). Apart from osteoporosis, NCCP and other pain conditions were also more prevalent in the extended high group albeit the proportions of residents with surgical wounds were not significantly different compared to other groups (p=0.1852). Relative to other groups, a statistically significantly higher proportion of extended high residents suffered from anxiety (44.6%), depression (60.2%), and manic depression (6.7%). Extended high residents with reports of resistance to care (7.0%) and physical behavioral problems (8.2%) were less common relative to other groups (p<0.0001). Compared to other groups, falls and severe cognitive impairment were also the least common in the extended high group (42.5% versus 44.6-48.1% in other groups, and 31.8% versus 37.0-46.0% in other groups, respectively).

*Table 11: Demographic and Clinical Characteristics in LTC Medicare Beneficiaries with Varying Patterns of Opioid Dose Over Time.*

| | Short-term, N=3,416 | Intermittent, N=1,855 | Restart, N=1,044 | Extended high, N=6,302 | Chi-squared |
|---|---|---|---|---|---|
| | N(%) | N(%) | N(%) | N(%) | p-value |
| Female Sex | 2,506(73.4) | 1,419(80.5) | 849(81.3) | 5,272(83.7) | <0.0001 |
| *Age Group* | | | | | |
| <65 years | 334(9.8) | 159(8.6) | 109(10.4) | 760(12.1) | <0.0001 |
| 65-74 years | 477(14.0) | 269(14.5) | 155(14.8) | 1,079(17.1) | |
| 75-84 years | 953(27.9) | 541(29.2) | 281(26.9) | 1,919(30.5) | |
| 85+ years | 1,652(48.4) | 886(47.8) | 499(47.8) | 2,544(40.4) | |
| Disability as OREC | 813(23.8) | 455(24.5) | 283(27.1) | 1,871(29.7) | <0.0001 |

*Table 11 continued: Demographic and Clinical Characteristics in LTC Medicare Beneficiaries with Varying Patterns of Opioid Dose Over Time.*

| | | | | | |
|---|---|---|---|---|---|
| *Race* | | | | | |
| Non-Hispanic | 2723(79.7) | 1494(80.5) | 849(81.3) | 5272(83.7) | <0.0001 |
| White | 381(11.2) | 207(11.2) | 119(11.4) | 695(11.0) | |
| Non-Hispanic | 193(5.6) | 106(5.7) | 49(4.7) | 220(3.5) | |
| Black | 111(3.2) | 47(2.5) | 26(2.5) | 100(1.6) | |
| Hispanic | | | | | |
| Other[1] | | | | | |
| Geographical | | | | | <0.0001 |
| Region | 658(19.3) | 332(17.9) | 147(14.1) | 998(15.8) | |
| Northeast | 477(14.0) | 243(13.1) | 168(16.1) | 892(14.2) | |
| West | 970(28.4) | 537(28.9) | 285(27.3) | 1950(30.9) | |
| Midwest | 1253(36.7) | 722(38.9) | 426(40.8) | 2376(37.7) | |
| South | | | | | |
| *Cognitive* | | | | | <0.0001 |
| *impairment* | 820(24.0) | 522(28.1) | 318(30.5) | 2,319(36.8) | |
| Intact | 784(23.0) | 450(24.3) | 228(21.8) | 1,429(22.7) | |
| Mild | 1,570(46.0) | 748(40.3) | 386(37.0) | 2,001(31.8) | |
| Moderate to | | | | | |
| Severe | | | | | |
| *Psychiatric* | | | | | |
| *disorders* | | | | | |
| Anxiety | 1092(32.0) | 674(36.3) | 379(36.3) | 2811(44.6) | <0.0001 |
| Depression | 1888(55.3) | 1043(56.2) | 601(57.6) | 3792(60.2) | <0.0001 |
| Manic Depression | 127(3.7) | 100(5.4) | 47(4.5) | 421(6.7) | <0.0001 |
| Psychotic | 445(13.0) | 272(14.7) | 149(14.3) | 831(13.2) | 0.2778 |
| disorder | | | | | |
| Schizophrenia | 181(5.3) | 103(5.6) | 54(5.2) | 296(4.7) | 0.3785 |
| PTSD | <11 | <11 | <11 | 24(0.4) | 0.6150 |
| *Persistent Pain* | 476(13.9) | 427(23.0) | 262(25.1) | 2,003(31.8) | <0.0001 |
| *NCCP* | | | | | |
| Chronic pain | 141(4.1) | 128(6.9) | 87(8.3) | 1098(17.4) | <0.0001 |
| Abdominal pain | 386(11.3) | 291(15.7) | 173(16.6) | 1134(18.0) | <0.0001 |
| Head and Neck | 579(16.9) | 454(24.5) | 259(24.8) | 1955(31.0) | <0.0001 |
| pain | | | | | |
| Limb pain | 11(0.3) | 12(0.6) | <11 | 59(0.9) | 0.0030 |
| Joint pain | 2619(76.7) | 1555(83.8) | 870(83.3) | 5356(85.0) | <0.0001 |
| Neuropathic pain | 419(12.3) | 273(14.7) | 153(14.7) | 1185(18.8) | <0.0001 |

[1] Other race includes Asian, Native American, and Other.

| *Table 11 continued: Demographic and Clinical Characteristics in LTC Medicare Beneficiaries with Varying Patterns of Opioid Dose Over Time.* | | | | | |
|---|---|---|---|---|---|
| *Other pain conditions* | | | | | |
| Osteoporosis | 500(14.6) | 248(13.4) | 126(12.1) | 871(13.8) | <0.0001 |
| Fracture | 87(2.5) | 73(3.9) | 21(2.0) | 140(2.2) | 0.0004 |
| Pressure ulcers | 307(9.0) | 192(10.4) | 112(10.7) | 741(11.8) | 0.0004 |
| Surgical wounds | 63(1.8) | 38(2.0) | 23(2.2) | 158(2.5) | 0.1852 |
| Pain effects sleep | 240(7.0) | 206(11.1) | 132(12.6) | 1200(19.0) | <0.0001 |
| Pain effects activity | 300(8.8) | 267(14.4) | 151(14.5) | 1432(22.7) | <0.0001 |
| *Behavioral Problems* | | | | | |
| Verbal | 549(16.1) | 298(16.1) | 156(14.9) | 1002(15.9) | <0.0001 |
| Physical | 383(11.2) | 183(9.9) | 107(10.2) | 519(8.2) | <0.0001 |
| Wandering | 688(20.1) | 342(18.4) | 192(18.4) | 1205(19.1) | 0.3771 |
| Resistance to Care | 335(10.0) | 183(10.0) | 91(8.7) | 428(7.0) | <0.0001 |
| *Other Conditions* | | | | | |
| Falls | 1525(44.6) | 879(47.4) | 502(48.1) | 2678(42.5) | <0.0001 |
| Delirium | 637(18.6) | 323(17.4) | 200(19.2) | 1110(17.6) | 0.3932 |
| Constipation | 143(4.2) | 72(4.0) | 54(5.2) | 329(5.2) | 0.0292 |

Other pain treatment characteristics

Table 12 summarizes other pain treatment characteristics identified among the total cohort and across the four identified groups. Almost half (42.8%) of residents were reported as receiving both scheduled and PRN pain medications and about a third were reported as receiving non-pharmacological pain treatment (33.6%). Only 18.6% had evidence of opioid use in the month prior to initiating opioid therapy in the nursing home. Most opioids used were oral formulations (98.6%); the most common opioid products were hydrocodone (54.2%), tramadol (36.8%) and oxycodone (17.7%). Pain adjuvant use was also found in 40.7% of residents; anticonvulsant pain adjuvants were the most common agent prescribed (23.9%).

Compared to other groups, scheduled pain medications, non-pharmacological pain treatments, and pain adjuvant medications were the most prevalent in the extended high group (Table 12). Also, evidence of opioid use prior to therapy initiation in the nursing home was significantly more common in the extended high dose group (84.7% vs. 44.5-67.3% in other groups, $p<0.0001$). Receiving only PRN pain treatment was less common in the extended high group compared to other groups (10.9% versus 20.0-24.5% in other groups, $p<0.0001$). More than half of residents in the extended high group received both scheduled and PRN pain treatment (55.1%). While hydrocodone was the most common opioid formulation used across all groups, the use of other formulations, except for codeine, were more common in the extended high dose group ($p<0.0001$). Relative to other groups, use of topical and transdermal opioid formulations were also more common in the extended high dose group (16.3% vs. 0.4-8.9% and 15.4% vs. 6.6-11.6%; $p<0.0001$).

*Table 12: Pain treatment characteristics among LTC Medicare beneficiaries receiving varying opioid dose trajectories over 180 days.* [1]

| | Total Cohort, N=12,582<br><br>N (%) | Shot-term, N=3,416<br><br>N (%) | Intermittent, N=1,855<br><br>N (%) | Restart, N=1,044<br><br>N (%) | Extended high dose, N=6,302<br><br>N (%) |
|---|---|---|---|---|---|
| Only scheduled pain medication reported | 3,091(24.5) | 694(20.3) | 339(18.3) | 195(18.7) | 1,863(29.6) |
| Only PRN pain medication reported | 2,073(16.4) | 684(20.0) | 448(24.2) | 256(24.5) | 685(10.9) |
| Both PRN and scheduled pain medication reported | 5,397(42.8) | 825(24.2) | 663(35.7) | 437(41.9) | 3,472(55.1) |
| Non-drug pain treatment | 4,243(33.6) | 820(24.0) | 568(30.6) | 365(35.0) | 2,490(39.5) |

*Table 12 continued: Pain treatment characteristics among LTC Medicare beneficiaries receiving varying opioid dose trajectories over 180 days.* [1]

| | | | | | |
|---|---|---|---|---|---|
| Prior Opioid Use | 2,342(18.6) | 219(6.4) | 236(12.7) | 125(12.0) | 1,762(28.0) |
| *Any Pain-adjuvants* | 5,138(40.7) | 1,023(29.9) | 679(36.6) | 407(39.0) | 3,029(48.1) |
| AD | 1,701(13.5) | 307(9.0) | 202(10.9) | 123(11.8) | 1,069(17.0) |
| SMR | 1,451(11.5) | 274(8.0) | 181(9.8) | 108(10.3) | 888(14.1) |
| AC | 3,021(23.9) | 538(15.7) | 370(19.9) | 211(20.2) | 1,902(30.2) |
| Steroids | 703(5.6) | 136(4.0) | 101(5.4) | 74(7.1) | 392(6.2) |
| *Opioid formulation* | | | | | |
| tramadol | 4,638(36.8) | 1,069(31.3) | 751(40.5) | 432(41.4) | 2,386(37.9) |
| oxycodone | 2,236(17.7) | 443(13.0) | 297(16.0) | 140(13.4) | 1,356(21.5) |
| morphine | 550(4.4) | 90(2.6) | 35(1.9) | 38(3.6) | 387(6.1) |
| fentanyl | 1,129(8.9) | 15(0.4) | 59(3.2) | 25(2.4) | 1,030(16.3) |
| hydrocodone | 6,843(54.2) | 1,744(51.1) | 977(52.7) | 580(55.6) | 3,542(56.2) |
| codeine | 578(4.6) | 190(5.6) | 105(5.7) | 63(6.0) | 220(3.5) |
| other | 261(2.1) | 22(0.6) | 23(1.2) | <11 | 207(3.3) |
| *Opioid route* | | | | | |
| oral | 12,438(98.6) | 3,406(99.7) | 1,844(99.4) | 1,044(100) | 6,144(97.5) |
| topical | 1,466(11.6) | 225(6.6) | 175(9.4) | 94(9.0) | 972(15.4) |
| transdermal | 1,129(8.9) | 15(0.4) | 59(3.2) | 25(2.4) | 1,030(16.3) |
| other | <11 | <11 | <11 | <11 | <11 |

[1] Except for other opioid routes of administration (which had a very small sample size), all chi-squared tests comparing proportions across groups yielded significant p-values ($p<0.0001$).

Multinomial regression analysis

Adjusted odds ratios with short-term as the reference group for all resident factors included in our multinomial regression analysis are reported in Table 13. Included in our adjusted model were sex, race, prior of use of opioid, pain adjuvant use (antidepressants, anticonvulsants, skeletal muscle relaxants, and steroids), non-pharmacological treatments, select pain-related diagnoses (osteoporosis, previous fracture, pressure ulcers), select chronic pain diagnoses (general chronic pain, chronic abdominal pain, chronic head and neck pain, chronic joint pain), select psychiatric diagnoses (anxiety,

manic depression, and schizophrenia), cognitive impairment, U.S. geographical region, delirium, wandering, falls and report of pain effecting sleep or activity.

Differences in the adjusted odds by sex, geographical U.S. region, and race in the intermittent, restart, and extended high group compared to the short-term group were found (Table 13). Relative to the short-term group, we found a significant inverse association between female sex and then extended high group compared to the short-term group (aOR[95%CI]= 0.82[0.74-0.92]). Relative to non-Hispanic White residents, increased odds of extended high group membership compared to short-term membership was also found (aOR[95%CI]=1.18[1.02-1.37]). Relative to the South U.S. region, decreased odds of residence in the Northeast(aOR[95%CI]=0.65[0.52-0.80]) and Midwest(aOR[95%CI]=0.80[0.67-0.95]) was associated with restart group membership compared to short-term group membership.

Strong associations were found between groups and pain diagnoses and treatments (Table 13). For example, relative to the short-term group residents, prior opioid users had 441% increased odds of being in the extended high group (aOR[95%CI]=4.41[3.79-5.15]). Odds of antidepressants (aOR[95%CI]=1.34[1.15-1.55]), skeletal muscle relaxants (aOR[95%CI]= 1.18[1.01-1.38]), steroids(aOR[95%CI]=1.27[1.02-1.57]), and non-pharmacological pain treatments(aOR[95%CI]=1.73[1.56-1.91]) were also more prevalent in extended high residents compared to those receiving short-term therapy. Chronic pain conditions mirrored these associations with significantly higher odds of chronic pain (aOR[95%CI]=3.19 [2.63-3.85]), abdominal pain (aOR[95%CI]= 1.35[1.18-1.55]), head

and neck pain (aOR[95%CI]= 1.59[1.42-1.78]) and joint pain diagnoses (aOR[95%CI]=1.35 [1.20-1.51]) relative to the short-term group.

Strong associations between cognitive impairment and psychiatric disorders and the extended high group were also found (Table 13). An inverse association between mild or moderate(aOR[95%CI]=0.78 [0.69-0.89]) and severe cognitive impairment (aOR[95%CI]= 0.69 [0.61-0.78]) with the extended high group relative to the short-term group was found. While compared to the short-term group, increased odds of extended high therapy was associated with anxiety(aOR[95%CI]= 1.49 [1.35-1.64]) and manic depression(aOR[95%CI]= 1.50 [1.20-1.88]).

*Table 13: Resident characteristic adjusted odds ratios of group membership relative to the short-term group.*

| | Intermittent, N=1,855 aOR(95%CI) | Restart, N=1,044 aOR(95%CI) | Extended high, N=6,302 aOR(95%CI) |
|---|---|---|---|
| *Prior Opioid Use* | 1.96(1.61-1.38) | 1.78(1.41-2.26) | 4.41(3.79-5.15) |
| *Pain Adjuvant Medication Use* | | | |
| Antidepressant | 1.06(0.87-1.28) | 1.12(0.89-1.41) | 1.34(1.15-1.55) |
| Skeletal Muscle Relaxant | 1.06(0.86-1.30) | 1.06(0.83-1.35) | 1.18(1.01-1.38) |
| Anticonvulsant | 1.14(0.98-1.33) | 1.10(0.91-1.32) | 1.54(0.98-1.33) |
| Steroid | 1.27(0.97-1.66) | 1.63(1.21-2.19) | 1.27(1.02-1.57) |
| *Non-pharmacological Pain Treatment* | 1.30(1.14-1.48) | 1.61(1.34-1.88) | 1.73(1.56-1.91) |
| *Male vs. Female Sex* | 0.88(0.76-1.00) | 1.03(0.87-1.21) | 0.82(0.74-0.92) |
| *Geographical Region (reference=south)* | 0.81(0.71-0.92) | 0.65(0.52-0.80) | 0.87(0.74-1.02) |
| Northeast | 0.92(0.77-1.11) | 1.08(0.87-1.34) | 1.07(0.92-1.24) |
| West | 0.93(0.81-1.08) | 0.80(0.67-0.95) | 0.94(0.84-1.06) |
| Midwest | | | |
| *Race (reference= non-Hispanic White)* | | | |
| non-Hispanic Black | 1.08(0.89-1.30) | 1.05(0.84-1.33) | 1.18(1.02-1.37) |
| Hispanic | 1.09(0.84-1.40) | 0.82(0.59-1.14) | 0.70(0.56-0.87) |
| Other | 0.85(0.59-1.21) | 0.74(0.48-4.46) | 0.53(0.39-0.72) |

*Table 13 continued: Resident characteristic adjusted odds ratios of group membership relative to the short-term group.*

| | | | |
|---|---|---|---|
| *Cognitive impairment (reference=intact)* | | | |
| Mild to Moderate | 0.95(0.81-1.12) | 0.79(0.64-0.96) | 0.78(0.69-0.89) |
| Severe | 0.85(0.73-1.00) | 0.72(0.60-0.87) | 0.69(0.61-0.78) |
| *Psychiatric disorders* | | | |
| Anxiety | 1.13(1.00-1.28) | 1.14(0.98-1.32) | 1.49(1.35-1.64) |
| Manic Depression | 1.35(1.02-1.79) | 1.08(0.76-1.55) | 1.50(1.20-1.88) |
| Schizophrenia | 1.03(0.80-1.34) | 0.97(0.70-1.34) | 0.82(0.66-1.01) |
| *NCCP* | | | |
| Chronic pain | 1.44(1.12-1.85) | 1.72(1.30-2.28) | 3.19(2.63-3.85) |
| Abdominal pain | 1.33(1.13-1.57) | 1.41(1.15-1.72) | 1.35(1.18-1.55) |
| Head and Neck pain | 1.39(1.21-1.61) | 1.39(1.72-1.66) | 1.59(1.42-1.78) |
| Joint pain | 1.37(1.14-1.65) | 1.37(1.14-1.65) | 1.35(1.20-1.51) |
| *Other pain conditions* | | | |
| Osteoporosis | 0.80(0.67-0.95) | 0.75(0.60-0.93) | 0.81(0.71-0.93) |
| Fracture | 1.66(1.20-2.29) | 0.89(0.55-1.45) | 1.05(0.78-1.40) |
| Pressure ulcers | 1.23(1.01-1.49) | 1.33(1.05-1.67) | 1.42(1.22-1.65) |
| Pain affected sleep | 1.19(0.94-1.50) | 1.43(1.09-1.87) | 1.59(1.33-1.91) |
| Pain affected activity | 1.36(1.10-1.67) | 1.20(0.93-1.10) | 1.63(1.38-1.92) |
| *Other Conditions* | | | |
| Wandering | 1.10(0.90-1.35) | 0.96(0.74-1.25) | 0.88(0.74-1.04) |
| Falls | 1.08(0.96-1.22) | 1.17(1.01-1.36) | 0.88(0.80-0.97) |
| Delirium | 0.95(0.80-1.11) | 1.16(0.96-1.41) | 1.12(0.99-1.27) |

Discussion

To our knowledge, this is the first study to use trajectory-based modeling to identify varying opioid dose patterns over time in the long-stay nursing home population. Patterns differed in average MEDD, duration of therapy, direction of dose change, and magnitude of dose change. Among LTC residents, the most common pattern found was extended high group (49.9%), followed by the short-term group (27.1%), the intermittent group (14.7%) and the restart group (8.3%). Extended high opioid therapy was found to be highly associated with chronic pain conditions diagnoses and the use of other pain treatments suggesting that longer durations of opioid use were associated with chronic pain syndromes.

High dose (over 90 MEDD) and long-term (greater than 90 days) opioid therapy are often cautioned against in guidelines citing increased overdose and fall-related risks.[3,25] Relative to the community counterparts, the risks might be even greater in the often older, frailer, and multimorbid LTC population.[1,40,89] While no known study has assessed the risks of falls and sedation in LTC residents receiving long-term opioid therapy, studies in older adults with chronic pain indicate increased risk of opioid overdose.[69] As well, studies accessing high opioid dose therapy and its association with falls and fractures indicate elevated risks at thresholds lower than 90 morphine milligram equivalents. One study assessing central nervous system medication burden in older nursing home residents, found an 83% increase in odds of serious falls among residents receiving three-times the standardized daily dose burden of centrally sedating medications (equivalent to about 30 MEDD) compared to those with no exposure.[44] Another study of 2,341 adults over the age of 60 with chronic non-cancer pain found a two-fold increase in fracture risk among those receiving ≥ 50MEDD compared to those with no exposure.[90] Given the prevalence of extended high opioid use in LTC, more research on safety risks associated with high dose and long-term opioid treatment in this population are needed.

Consistent with previous literature, we found female sex, lack of cognitive impairment, and use of pain adjuvants and non-pharmacological pain treatments associated with opioid therapies greater than 90 MEDD and spanning more than 90 days.[16,17] We also found variations by U.S. geographic region.[52] Unlike previous studies, we found non-Hispanic Black race to have increased odds of extended high dose opioid therapy[16,17] Differences in cohort selection, time periods, and inclusion of different

covariates in analyses likely explain different findings; our study used an enhanced variable to identify race, was not limited to individuals over the age of 65 years and covariates describing marital status, education, and total comorbidity burden were not included in our study.

Inconsistent findings also might be due to incongruence of definitions of long-term therapy to extended high opioid therapy. While the CDC defines long-term opioid therapy as opioid treatment where supply covers "most" days over a three month period,[91,1] the few previous studies assessing opioid therapy duration in nursing home residents defined long-term opioid use as 90 days of opioid exposure over a 120 day follow-up period.[16,17] Individuals in our extended high dose group received, on average, 73.6 days (median: 68 days) of opioid therapy over the 180 follow-up period; while consistent with a CDC definition, the definition used in previous nursing home literature would not flag individuals with this pattern as "long-term." Assuming extended high dose opioid use is associated with opioid-related safety risks, studies evaluating associations between long-term therapy using a 90-days over 120-days definition might attenuate calculated risks by including high risk individuals who do not meet the cut offs in their comparison group.

There are several limitations to this study and to the use of LCGM. To ensure we would be able to describe opioid exposure throughout the follow-up period, we required all residents be followed for 180 days. Sicker residents with hospitalizations or death were excluded. We chose to run analyses in this possibly healthier subset of LTC residents to reduce the high degree of bias that missing data cause in LCGM.[73] Like all claims-based analyses, we assumed opioids were used as prescribed; it is possible that

titration schedules we're unable to access were provided alongside prescriptions. Also, we likely underestimated opioid use prior to nursing home admission as we were not able to identify hospitalization-related opioid use. Our look-back period to identify prior opioid use of 30 days was longer than the national average for hospitalization stay-length (about five days)[80] and therefore likely captured prior opioid use outside of the hospital. Lastly, the latent class growth modeling classified the participants into heterogenous groups based on the growth of opioid use over time, without accounting for the variation in the growth within each class.

Our study also had several strengths. This is the first known study to used LCGM, a person-centered analysis strategy, to identify different opioid dose patterns over time in the nursing home population. Our study used both claims and MDS survey data to aid in assessment of several resident characteristics that might impact receipt of opioid therapy. We used an enhanced race measure with positive predictive values of 98.7%, 95.9%, and 84.8% for identifying Non-Hispanic White, Non-Hispanic Black, and Hispanic races, respectively.[14] We identified pain adjuvant medication, PRN pain, and non-pharmacological pain treatment use to provide a comprehensive understanding of how LTC resident's pain is treated. Common pain conditions associated with opioid therapy were identified to see what conditions likely lead to opioid use. Finally, we did not limit our study to certain opioid products; we included combination and non-oral formulations.

## Conclusion

Nursing home residents are a vulnerable population with a high rate of opioid use. Using LCGM, we identified four patterns of opioid use in LTC beneficiaries that simultaneously considered individuals' opioid duration, dose, and change in dose over a

180-day period. Residents with the highest probability of assignment to each group were found to vary demographically and clinically. More research is needed to evaluate how varying opioid dosing strategies over time are associated with health-related outcomes in LTC residents.

**Aim 3: Opioid dosing over time and falls among long-term care nursing home residents: a latent class analysis.**

Abstract

Background/objectives: Analgesic tolerance, disease progression, side-effects, and acute illness episodes are frequent in nursing home residents and could lead to opioid dosing patterns. No known study has accessed the odds of fall across different opioid dosing patterns over time.

Methods: This 2011-2015 longitudinal study included 11,015 LTC residents receiving opioid therapy from a 5% national sample of Medicare beneficiaries. Latent class growth modeling (LCGM) identified patterns of average morphine equivalent daily dose (MEDD) across six 30-day intervals. Adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) from a facility clustered generalized estimating equation model quantified the association between different opioid dosing patterns and falls.

Results: Four patterns of opioid dose over time were identified: LTC residents received either short-term (27.0%), intermittent (14.7%), restart (8.3%), or extended high opioid therapies (49.5%). While the odds of falls were similar in those receiving short-term and extended high dose opioid patterns, elevated odds of falls were observed in those restarting opioids (aOR: 1.15; 95% CI: 0.99-1.35) and those with intermittent opioid use (aOR: 1.17; 95% CI: 1.03-1.32) relative to those with a high extended high dose opioid pattern. Additional analyses in samples restricted to residents with high membership probabilities and new users of opioids found consistent results, albeit with varying statistical significance.

Conclusions: Different opioid use patterns over time may affect the odds of incident falls. Additional studies accessing the magnitude by which opioids-related safety risks are attenuated or exacerbated by varying opioid dosing strategies in LTC nursing home residents are needed.

## Introduction

Falls are common in long-term care nursing home (LTC) residents. An estimated 1.7 falls occur in LTC residents annually[92,93] and these falls are often associated with serious injury (i.e., fractures or traumatic brain injury), psychological distress, lower quality of life, high healthcare costs, and death.[92–94] Opioids are thought to increase fall risk through their sedative effects.[93] Relative to older adults without opioid use, older opioid users are at a 15%, 40%, and 71% increased risk of fall, fall-injury and fracture, respectively.[95] A pooled analysis indicates opioid-related fall risk is dosage dependent, with higher doses incurring greater risk.[95] This increase in fall risk is a major reason why the American Geriatrics Society Beers Criteria Update Expert Panel advised clinicians to reserve opioid therapy for only severe acute pain in older adults.[3,96] Given the high prevalence of opioid use and the morbidity and mortality associated with falls, a complete understanding of how opioid use affects fall risk is needed.[52]

Studies accessing opioid-related risks in nursing home populations using summary measures of exposure that assume consistent use over a set period of time might be grouping residents with varying levels of opioid tolerance.[74–77] Progression of disease and episodes of acute illness common in this population could lead to frequent changes in opioid therapy, which might affect a resident's ability to develop opioid tolerance.[68] Opioid tolerance, or the decreased sedating and analgesic effects produced at a certain

dose after three weeks of continuous therapy,[79] might explain some variations in opioid-related risks associated with the sedating effect of opioids. For example, an individual initiated on moderate dose therapy without an opportunity to develop tolerance could have lower risk of opioid-related safety risks than someone who was slowly titrated over several weeks to a high dose.

A review of animal studies regarding opioid tolerance suggests there might be age-related declines in opioid tolerance development.[78] The magnitude of this decrease is unclear. If tolerance does play a role in opioid risks among long-term nursing home residents, more complex parameters around opioid use appropriateness may be warranted.

In the following study, we applied latent class group modeling (LCGM) to Medicare claims and the Minimum Dataset 3.0 to evaluate whether different opioid dose patterns affected odds of fall. We hypothesized we would find higher odds of falls in less stable dosing patterns over time (i.e., patterns with sudden increases or discontinuations) where tolerance was less likely to have developed relative to more stable opioid dosing regimens.

## Methods

### Study design and data source

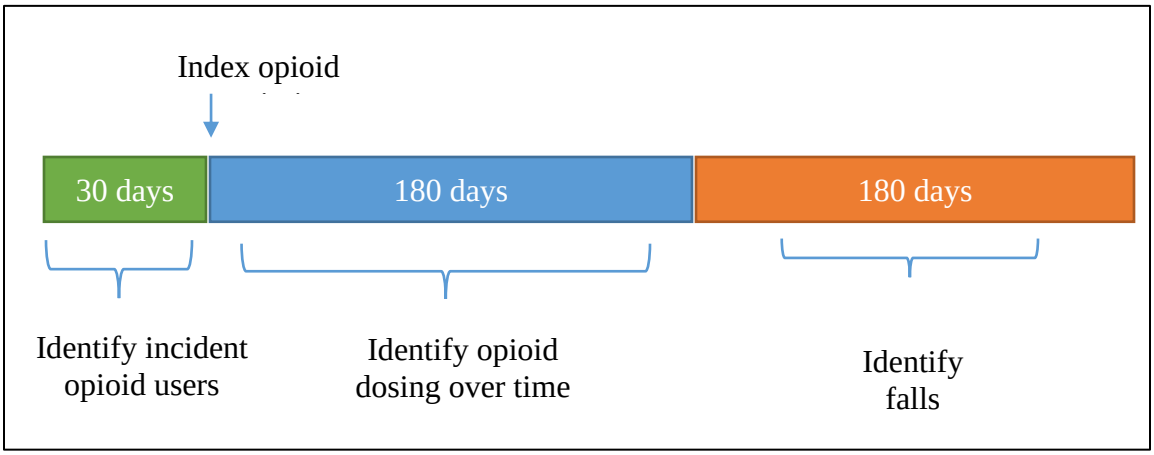
To accurately characterize opioid and resident characteristics, this retrospective longitudinal study used data from Medicare Parts A, B and D claims and the Minimum Dataset 3.0 (MDS) from January 1st, 2011 to December 31st, 2015. Medicare Parts A, B and D claims provided all fee-for-service institutional and non-institutional claims and enrollment/eligibility information for a nationally representative 5% sample of Medicare

beneficiaries. Claims were used to identify falls, characterize opioid exposure, and identify residents with chronic pain diagnoses. MDS, a federally mandated quarterly survey describing nursing home resident's health and healthcare utilization, identified beneficiaries residing long-term in nursing homes, falls not resulting in emergency room or hospitalization visits, as well as additional resident clinical and demographic characteristics.

Study sample

For our study, we followed all LTC Medicare beneficiaries with at least one opioid prescription starting either upon entry into the nursing home or 30 days prior to the first opioid prescription (i.e., the index date) admitted to a nursing home from 2011 to 2015. Residents were then followed for 360 days (Figure 6). Opioid dosing patterns were identified during the exposure window or the first 180 days following the first opioid prescription. Falls were identified during the follow-up period or the subsequent 180-days following the exposure window. An additional 30-day look back period allowed for differentiation between prevalent and incident opioid users. Consistent with previous literature, Medicare beneficiaries were identified as LTC if the total days between admissions and discharge (or the last available assessment date) after subtracting days associated with SNF services was at least 100 days. [46–48]

*Figure 6: Follow-up of residents in cohort.*




Additional inclusion criteria included continuous enrollment in Medicare Parts A, B, and D during the 360-day study period and for at least 30-days prior to the index opioid prescription. Continuous coverage allowed for accurate identification and characterization of LTC residents, opioid use, and fall-related hospitalizations. Residents with stays associated with hospice care or with Medicare Advantage insurance during the stay were excluded. From our 5% sample, we found 11,015 eligible LTC residents for our study.

Opioid use

Starting with the first opioid prescription dispensing date, we identified the average morphine equivalent daily dose (MEDD) across 6 discrete 30-day intervals. All prescription medications identified from Medicare part D claims are reported in supplemental Table 14. MEDD was calculated by multiplying the strength per unit in milligrams by the average daily units dispensed and the oral morphine equivalent conversion factor(OME).[54] We capped MEDD at 180 mg/day to prevent individual extreme prescriptions from inflating our calculations. We chose 180mg/day because it is

twice the 90 mg daily dosing cautioned against in the 2016 CDC guidelines on prescribing opioids for chronic pain and three times the threshold for high-dose therapy (50 MEDD) used in literature evaluating nursing home residents.[1,16] To calculate average MEDD per interval, we summed all MEDD per interval then divided by the number of interval days that resident received opioid therapy (Equation 1).

*Equation 1: Equation for calculating average MEDD per interval from Medicare part D claims.*

$$\frac{\sum((\frac{strength(mg)}{unit}) * (\frac{units\ dispensed}{days'supply}) * interval\ days * OME\ conversion\ factor)}{opioid\ days}$$

Here "days' supply" refers to the prescription therapy length in days, "interval days" refers to the prescription treatment days that fall within each interval, and "opioid days" refers to the total unique number of days across all prescriptions within each interval that opioids were supplied. All day values were based on prescription dispensing dates and days' supply. While calculating days' supply and opioid days, we assumed overlapping prescriptions of ≥ 1 day were used simultaneously. Conversion factors were based on those used by the Centers of Medicare and Medicaid Services.[54] Prevalent opioid users had opioid prescriptions dispensed during the 30 days prior to the first opioid prescription seen in the nursing home.

*Table 14: Opioid and non-opioid pain and pain adjuvant medications searched for in Medicare part D claims.*[6,55]

| Category | Generic drugs included |
|---|---|
| Opioids and opioid combination products | albuphine, buprenorphine, buprenorphine combination products, codeine, codeine combination products, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, oxycodone, levorphanol, meperidine, methadone, morphine, nalbuphine, oxymorphone, pentazocine, tapentadol, tramadol and opioid combination products |
| Skeletal Muscle Relaxants (SMR) | baclofen, carisoprodol, chlorzoxazone, clonazepam, cyclobenzaprine, metaxalone, tizanidine |
| Anticonvulsants (AC) | carbamazepine, gabapentin, pregabalin, lamotrigine |
| Systemic corticosteroids | betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, triamcinolone |
| Antidepressants (AD) | amitriptyline, amitriptyline-chlordiazepoxide, amitriptyline-perphenazine, desipramine, imipramine, nortriptyline, duloxetine, venlafaxine, milnacipran |

Fall events

Resident who did and did not fall were identified using MDS assessment and/or emergency room or hospital claims during the follow-up period. We identified falls reported in MDS using variable J1800 which asks if residents have fallen since their last assessment. An estimated 62.9% and 82.0% of all and serious falls are reported by J1800.[97] Emergency department (ED) and hospitalizations associated with fall-injury were captured using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) and external cause of injury (e-codes) according to an algorithm developed and validated in Medicare data.[98] Relative to capturing falls using only injury e-codes, an algorithm incorporating both ICD-9-CM claims and e-codes accurately captures 21% more fall-injury events.[98]

Covariates

Residential characteristics that could explain variations in opioid dosing were identified from MDS assessments and Medicare claims. Age, sex, race, U.S. geographical region, and original reason for Medicare entitlement (OREC) associated with each LTC beneficiary were pulled from the annual CCW Master Beneficiary File corresponding to the first opioid prescription. Resident age was grouped into 10-year increments (<65, to 74, 75 to 84, and >85 years of age and older). Race was based on a modified race variable that classified beneficiaries as Hispanic or Asian race if their first or last name, according to the RTI algorithm, was likely associated with origin from those places.[14] Race was grouped into four categories: non-Hispanic White, non-Hispanic Black, Hispanic, and other. Other included residents reported as Asian and Native American, these groups were less than 1% each. The three categories for OREC were grouped to create two categories: disability (end stage renal disease and disability) and age.

Average cognitive impairment, psychiatric disorders, behavioral problems (i.e., reports of aggressive behavior, verbal behavior, wandering and resistance to care), delirium, and constipation were identified from MDS assessments prior to the exposure period. Average cognitive ability was calculated by averaging all available Brief Inventory Mental Status Scores (BIMS) or Cognitive Performance Scales (CPS). BIMS is a resident-reported measure of cognition that categorizes individuals as cognitively intact (score =13-15), moderately impaired (score=8-12), or severely impaired (0-7). Some residents, namely those with cognitive impairment, might not have been able to participate in a BIMS assessment.[81] Among those residents with no available BIMS assessments, an average of the CPS, a staff-reported measure of resident cognition, was used to categorize residents as cognitively intact (score =0-2), moderately impaired

(score=2-4) or severely impaired (score=5-6).[83] Delirium was identified using the confusion assessment method (CAM) diagnostic algorithm.[85,86]

For persistent pain and chronic pain diagnoses, we extended the period for characterization to include the exposure window. Inclusions of claims and assessments occurring during the exposure period greatly reduced missingness and likely capture chronic pain conditions that first developed prior to opioid. Non-cancer chronic pain (NCCP) diagnoses were identified using ICD9 and ICD10 diagnoses consistent with previous literature (Supplemental Table 2). We defined persistent pain as two or more reports of pain on assessments at least 90 days apart.[31]

*Table 15: CD-9 CM and ICD-10 CM codes used to define chronic painful conditions from outpatient, skilled nursing, and physician claims.* [50,51]

| Painful conditions | ICD- 9 CM Definition | ICD-10 CM Definition |
|---|---|---|
| Chronic pain | 338.0, 338.2x, 338.4 | G89.0, G89.2x, G89.4 |
| Abdominal pain | 533.4x-533.9x, 550.x-553.x, 555.x, 556.x (except 556.4), 564.1, 569.42, 577.1x, 590.0x, 789.0x | K27.4-K27.9, K40.x-K46.x, K50.x, K51.x (except K51.4x), K58.x, K62.89, K86.0, K86.1, N11.x, R10.1x-R10.8 |
| Musculoskeletal pain | | |
| Back/neck pain | 720.x-724.x | M45.x-M55.x |
| Head | 307.81, 339.x, 346.x | G43.x, G44.x |
| Limb pain | 354.4, 355.71, 729.5 | G56.4x, G57.7x, M79.6x |
| Arthritis/rheumatism/ joint pain/myalgia | 274.x, 710.xx-719.xx, 725.x-729.x (excluding 729.5 and 729.2) | M1A.x, M05.x-M08.x, M11.x-M19.x, M22.x-M25.x, M65.x-M67.x, M70.x-M71.x, M75.x-M77.x, M79.x (except 79.6x and M79.2), M94.x |
| Neuropathic pain | 53.1x, 249.6x, 250.6x, 337.1, 337.2x, 340.x, 341.9, 350.x, 351.x, 353.x-356.x, 357.81, 729.2, 951.4, 952.x, 953.x | B02.23, E08.4x, G99.0, G90.5x, G35.x, G37.9, G50.x, G54.x, G56.x(except G56.4), G54.x-G58.x (except G57.7x), G61.81, M79.2, S04.50XA, S14.x, S24.x, S34.x |

Statistical Analysis

Latent class growth modeling was used to identify major classes of initial opioid dose trajectories. Models were generated in SAS Studio using the PROC TRAJ procedure.[88] For the model, the time scale included six 30-day periods (30 days was the most common opioid prescription length found in the data) starting with the first opioid prescription dispensed in the nursing home. The mean MEDD calculated from each interval was log transformed to deal with non-normal distributed data (skewness=16.65, kurtosis=594.50). Inclusion and exclusion criteria described previous ensured no missing opioid dose data during the exposure period.

Consistent with recommendations,[73,88] model fit was done in two stages. First, the optimal number of classes were identified by evaluating three criteria in seven censored models with one to seven fixed quadratic groups: changes in the Bayesian information criterion (BIC), a sufficient average group membership probability (>80%), and a sufficient proportion of patients in each group to permit meaningful analysis (i.e., >5% or n>680). Second, linear, quadratic, or cubic line fit was chosen based on best BIC. As a sensitivity analysis, we also identified trajectories in three restricted cohorts; one cohort limited to those with at least one seven-day opioid prescription during their follow-up period and another included only LTC residents who did not have opioid use in the month prior to their first observed opioid prescription in the nursing home. Residents were assigned to groups in which they had the highest probability of belonging. Mean, standard deviation (SD), and median MEDD among residents in each trajectory groups were calculated for each time interval. Chi-squared statistics were used to compare

demographic and clinical resident characteristics assigned to each identified dosing pattern.

Chi-squared statistics were used to compare group membership, pain treatment characteristics, demographical characteristics and clinical characteristics among residents who did and did not fall. Generalized estimating equations calculated facility clustered relative odds ratios of falls among residents with different patterns of opioid dose relative to risks in those receiving extended high-dose therapy. With stable continuous opioid treatment over a 180-day period, residents in the extended high dose group were the most likely group to have developed tolerance.[78] Stepwise covariate selection for the model was done using PROC HPGENSELECT.[99] Additional stratified sensitivity analyses were conducted. Analyses among only residents with high probability (>80%) of group membership were conducted to access if residents unlike the class they were assigned were affecting calculated relationship. Analyses among only new users of opioid therapy aimed to confirm associations among residents with complete opioid exposure history. All statistical analyses were performed using SAS version 9.4.

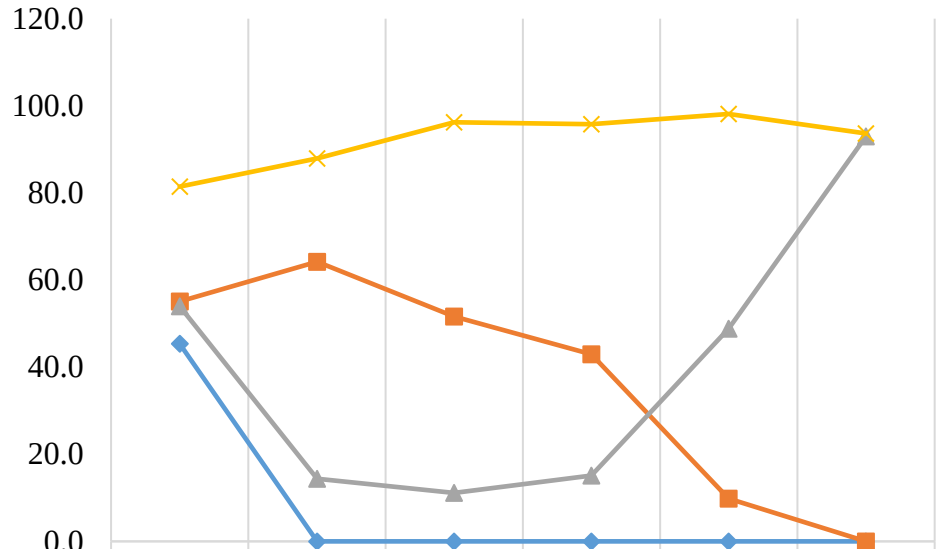
## Results

### Common Opioid Dosing Patterns

From the 11,015 LTC beneficiaries in our study, we identified four common patterns of opioid dosing over time; short-term, intermittent, restart and extended high dose groups (Figure 7). Most residents in our sample (49.9%) received MEDD across study intervals consistent with the extended high dose group. On average, extended high dose residents received between 81 and 98 MEDD across the six 30-day intervals. Short-term therapy was found in 27% of residents. Average MEDD among short-term residents

was 45 and treatment duration was less than 30 days. Almost one in seven (14.7%) residents received intermittent therapy characterized by, on average, MEDDs ranging from 10 to 63 over 150 days. Restart therapy where the average MEDD decreased from 54 to 12 across over the first 90-days then increased in average MEDD (from 12 to 93) over 90 days was found in 8.3% of residents. Additional descriptive information about the MEDD by interval and group are available in Table xvi.

*Figure 7: Table and graph of common patterns of opioid morphine milligram equivalent dose over 180-days identified among long-term care nursing home residents using latent class group modeling.*




| | Day 0 to 30 | Day 31 to 60 | Day 61 to 90 | Day 91 to 120 | Day 121 to 150 | Day 151 to 180 |
|---|---|---|---|---|---|---|
| Short-term | 45.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Intermittent | 55.1 | 64.2 | 51.6 | 43.0 | 9.8 | 0.0 |
| Restart | 54.0 | 14.4 | 11.1 | 15.1 | 48.8 | 93.0 |
| Extended high | 81.4 | 87.9 | 96.2 | 95.7 | 98.1 | 93.6 |

*Table 16: Mean, standard deviation and median of average morphine equivalent daily dose (MEDD), total days of opioid therapy, and time to opioid therapy initiation among LTC Medicare residents in varying opioid dose trajectory groups over the 180- day follow-up.*

| | Short-term, N=2,982 | Intermittent, N=1,617 | Restart, N=901 | Extended high dose, N=5,479 |
|---|---|---|---|---|
| | mean (SD), median | mean (SD), median | mean (SD), median | mean (SD), median |
| Pre-index 30 days | 2.2(11.5), 0 | 4.1(15.2), 0 | 4.8(19.4), 0 | 16.5(38.6), 0 |
| 0 to 30 days | 45.4(30), 30.0 | 55.1(52.5), 32.0 | 54.0(55.0), 30.0 | 81.4(63.7), 57.3 |
| 31 to 60 days | 0.0(0.0), 0.0 | 64.3(73.3), 20.0 | 14.4(42.8), 0.0 | 87.9(72.0), 75.0 |
| 61 to 90 days | 0.0(0.0), 0.0 | 51.6(70.9), 0.0 | 11.1(0.0). 0.0 | 96.2(71.2), 90.0 |
| 91 to 120 days | 0.0(0.0), 0.0 | 43.0(68.3), 0.0 | 15.1(44.5), 0.0 | 95.7(71.0), 87.0 |
| 121 to 150 days | 0.0(0.0), 0.0 | 9.8(0.0), 0.0 | 48.8(70.9), 0.0 | 98.1(70.6), 95.5 |
| 151 to 180 days | 0.0(0.0), 0.0 | 0.0(0.1), 0.0 | 93.0(75.2), 100.0 | 93.6(71.6), 85.6 |
| | | | | |
| Days of therapy | 8.9(8.0), 12.0 | 19.5(22.4), 10.0 | 19.7(23.5), 10.0 | 73.6(54.6), 68.0 |
| Days to therapy | 151.9(196.1), 84.5 | 110.2(159.9), 58.0 | 115.2(161.1), 64.5 | 75.6(126.9), 40.0 |

Demographic, clinical and pain-treatment characteristics across these common patterns of opioid dosing over time are summarized in Table 17. Briefly, the extended high group had the highest proportion of female (78.7% versus 73.0-76.9% in other groups), non-Hispanic White (83.4% versus 79.4-81.1% in other groups), disability OREC (30.6% versus 24.9-27.7% in other groups), and intact cognition (35.5% versus 23.0-30.5% in other groups) compared to proportions seen in other groups. Extended high residents were also more likely to have pain diagnoses and certain pain treatments with 60.0% having persistent pain, 91.2% with at a NCCP diagnosis, 28.4% with a prior opioid prescription, and 40.6% with non-pharmacological treatment of pain (Table 17).

*Table 17: Demographic and clinical characteristics among long-term care nursing home residents receiving varying average MEDD over 180-days.*

| | Short-term | Inter-mittent | Restart | Extended High | Chi-square |
|---|---|---|---|---|---|
| | N=2,982 | N=1,617 | N=901 | N=5,479 | p-value |
| Age | | | | | |
| Less than 65 years | 313(10.5) | 148(9.2) | 95(10.5) | 696(12.7) | <0.0001 |
| 65 to 74 years | 428(14.4) | 245(15.2) | 143(15.9) | 965(17.6) | |
| 75 to 84 years | 839(28.1) | 473(29.3) | 246(27.3) | 1,698(31.0) | |
| Over 85 years | 1,402(47.0) | 751(46.4) | 417(46.3) | 2,120(38.7) | |
| Female Sex | 2,177(73.0) | 1,244(76.9) | 658(73.0) | 4,311(78.7) | <0.0001 |
| Race/Ethnicity | | | | | |
| Non-Hispanic White | 2,368(79.4) | 1,292(79.9) | 731(81.1) | 4,572(83.4) | <0.0001 |
| Non-Hispanic Black | 338(11.3) | 186(11.5) | 106(11.8) | 614(11.2) | |
| Hispanic | 172(5.8) | 95(5.9) | 41(4.6) | 197(3.6) | |
| Other | 97(3.3) | 43(2.7) | 22(2.4) | 85(1.6) | |
| Disability as OREC | 743(24.9) | 413(25.5) | 250(27.7) | 1,674(30.6) | <0.0001 |
| Region | | | | | 0.0002 |
| Northeast | 572(19.2) | 293(18.1) | 129(14.3) | 848(15.5) | |
| West | 412(13.8) | 215(13.3) | 147(16.3) | 757(13.8) | |
| Midwest | 858(28.8) | 465(28.9) | 243(27.0) | 1,709(31.2) | |
| South | 1,095(36.7) | 627(38.8) | 366(40.6) | 2,085(38.1) | |
| Psychiatric Disorder | 1,617(54.2) | 1,190(53.0) | 512(56.8) | 3,102(56.6) | 0.0239 |
| *Cognitive Impairment* | | | | | <0.0001 |
| Intact | 685(23.0) | 466(28.8) | 275(30.5) | 1,944(35.5) | |
| Mild-moderate | 712(23.9) | 406(25.1) | 200(22.2) | 1,293(22.6) | |
| Severe | 1,120(37.6) | 478(49.6) | 268(29.7) | 1,381(25.2) | |
| Missing | 465(15.6) | 267(16.5) | 158(17.5) | 915(16.7) | |
| Behavioral Problem | 681(22.8) | 320(19.8) | 195(21.6) | 1,070(19.5) | 0.0027 |
| Persistent Pain | 729(24.4) | 700(43.3) | 408(45.3) | 3,290(60.0) | <0.0001 |
| NCCP | 2,493(83.6) | 1,439(89.0) | 806(89.5) | 4,996(91.2) | <0.0001 |
| Prior Opioid Prescription | 192(6.4) | 207(12.8) | 106(11.8) | 1,556(28.4) | <0.0001 |
| Pain-adjuvant | 911(30.5) | 607(37.5) | 348(38.6) | 1,665(30.4) | <0.0001 |
| *Medication use* | | | | | |
| Non-pharmacological Pain Treatment | 727(24.4) | 516(31.9) | 338(37.5) | 2,221(40.5) | <0.0001 |
| History of Fall | 1,415(47.5) | 830(51.3) | 466(51.7) | 2,764(50.4) | 0.0160 |
| Delirium | 311(10.4) | 150(9.3) | 97(10.8) | 481(8.8) | 0.0441 |
| Constipation | 130(4.4) | 71(4.4) | 33(3.7) | 279(5.1) | 0.0096 |

Residents Who Did and Did Not Fall

Characteristics among residents who did and did not fall are summarized in Table 18. Demographically, residents who fell were more likely older (p<0.0001), non-Hispanic white (p<0.0001), gained Medicare entitlement through age (p<0.0001), and reside in the Midwest (p<0.0001). Clinically, residents who fell were more likely to have cognitive impairment (p<0.0001) compared to those who did not fall.

Opioid dosing over time common among residents who fell and those who did not fall differed (p=0.0096). Evidence of fall was found in 40.0%, 37.3%, 34.9%, and 33.8% of residents receiving restart, intermittent, extended high, and short-term opioid dosing therapies, respectively. Prior opioid prescription, pain adjuvant medication use, and non-pharmacological treatments did not differ between those who did and did not fall.

*Table 18: Pain treatment, demographic and clinical resident characteristics among long-term care nursing home residents who did and did not fall in 180-day follow-up period.*

| | Residents who fell<br><br>N=3,892 | Residents who did not fall<br><br>N=7,123 | Chi-square p-value |
|---|---|---|---|
| Demographic Characteristics | | | |
| Age | | | |
| Less than 65 years | 344(27.5) | 908(72.5) | <0.0001 |
| 65 to 74 years | 561(68.5) | 1,220(68.5) | |
| 75 to 84 years | 1,198(63.2) | 2,058(36.8) | |
| Over 85 years | 1,770(62.3) | 2,920(37.7) | |
| Female Sex | 2,989(73.6) | 5,401(35.6) | 0.1679 |
| Race/Ethnicity | | | |
| Non-Hispanic White | 3,300(36.8) | 5,663 (63.2) | <0.0001 |
| Non-Hispanic Black | 328(26.4) | 916(73.6) | |
| Hispanic | 159(31.5) | 346(68.5) | |
| Other | 80(32.4) | 167(67.6) | |
| Disability as OREC | 953(30.9) | 2,127(69.1) | <0.0001 |
| Region | | | |
| Northeast | 606(32.9) | 1,236 (67.1) | 0.0035 |
| West | 532(34.7) | 999(65.3) | |
| Midwest | 1,222(37.3) | 2,053(62.7) | |
| South | 1,446(34.7) | 2,727(65.3) | |

*Table 18 continued: Pain treatment, demographic and clinical resident characteristics among long-term care nursing home residents who did and did not fall in 180-day follow-up period*

| | | | |
|---|---|---|---|
| Psychiatric disorder | 3,811(37.4) | 3,811(62.6) | <0.0001 |
| Cognitive impairment | | | <0.0001 |
| Intact | 994(29.5) | 2,376(70.5) | |
| Mild-moderate | 961(37.6) | 1,596(22.5) | |
| Severe | 1,306(40.2) | 1,941(27.3) | |
| Missing | 1,193(66.1) | 612(8.6) | |
| Behavioral Problem Reported | 998(44.0) | 1,268(56.0) | <0.0001 |
| Persistent Pain | 1,811(35.3) | 3,316(64.7) | 0.9242 |
| NCCP | 3,473(35.7) | 6,261(64.3) | 0.0136 |
| Prior opioid prescription | 733(35.6) | 1,328(64.4) | 0.7608 |
| Pain adjuvant medication use | 1,600(35.3) | 2,931(64.7) | 0.9474 |
| Non-pharmacological pain treatment | 1,339(35.2) | 2,463(64.8) | 0.9261 |
| History of Fall | 2,382(43.5) | 3,093(56.5) | <0.0001 |
| Delirium | 460(44.3) | 579(55.7) | <0.0001 |
| Constipation | 191(37.2) | 322(62.8) | 0.3424 |
| Opioid Dosing Pattern Group | | | |
| Short-term | 1,008(33.8) | 1,974(66.2) | 0.0096 |
| Intermittent | 603(37.3) | 1,014(62.7) | |
| Restart | 351(40.0) | 550(61.0) | |
| Extended high dose | 1,911(34.9) | 3,568(65.1) | |

Opioid Dosing Over Time and Odds of Fall

Unadjusted and adjusted analyses are reported in Table 19. Our final model included 9 covariates; fall history, age, race, region, psychiatric disorder, cognitive impairment, behavioral disorders, NCCP, and prior opioid exposure. Unadjusted models identified a 19% increase in falls (95% CI=1.03-1.38) in the restart group and a notable albeit insignificant 11% increase in falls (95%CI=0.99-1.24) relative to the extended high group. Adjusted analyses were consistent with unadjusted findings.

Unadjusted and adjusted odds ratios from our additional stratified analyses are also summarized in Table 19. Models limited to residents with high probability of group membership (>80%) yielded similar findings with the association between the

intermittent group and falls becoming slightly more significant. Models limited to new users of opioid therapy were also similar albeit slightly less significant.

*Table 19: Unadjusted and resident characteristic adjusted odds ratios of falls during the 180-day follow-up period among residents with varying opioid dosing patterns relative to those receiving extended high dose therapy.*

| | Unadjusted Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio (95% Confidence Interval) |
|---|---|---|
| Total (N=10,979) | | |
| Short-term | 0.95(0.87-1.05) | 0.98(0.89-1.09) |
| Intermittent | 1.11(0.99-1.25) | 1.13(1.00-1.27) |
| Restart | 1.19(1.03-1.38) | 1.19(1.03-1.39) |
| Extended high dose | Reference | Reference |
| High Probability Membership (N=10,434) | 0.96(0.87-1.05) | 0.98(0.89-1.09) |
| Short-term | 1.14(1.01-1.29) | 1.14(1.01-1.31) |
| Intermittent | 1.20(1.03-1.41) | 1.21(1.03-1.41) |
| Restart | Reference | Reference |
| Extended high dose | | |
| New User (N=8,918) | | |
| Short-term | 0.97(0.87-1.07) | 1.00(0.90-1.12) |
| Intermittent | 1.13(1.00-1.29) | 1.16(1.01-1.32) |
| Restart | 1.14(0.97-1.33) | 1.13(0.97-1.33) |
| Extended high dose | Reference | Reference |
| New User High Probability (N=8,459) | | |
| Short-term | 0.96(0.87-1.07) | 1.00(0.89-1.12) |
| Intermittent | 1.17(1.02-1.34) | 1.19(1.03-1.37) |
| Restart | 1.13(0.96-1.34) | 1.14(0.96-1.35) |
| Extended high dose | Reference | Reference |
| Only residents > 64 years (N=9,727) | | |
| Short-term | 0.93(0.84-1.02) | 0.96(0.86-1.07) |
| Intermittent | 1.08(0.96-1.23) | 1.12(0.99-1.27) |
| Restart | 1.17(1.00-1.36) | 1.18(1.01-1.39) |
| Extended high dose | Reference | Reference |

Discussion

Of the 11,015 LTC residents followed in our study, almost half (49.8%) received extended high therapy (i.e., continuous therapy of around 90 morphine milligram equivalents for 180 days) and about one in three (35.3%) fell. Consistent with our theory

that steady and continuous exposure to opioids would result in tolerance to sedating effects, no difference in odds of falls were found among residents with short-term and extended high opioid dosing patterns. Models did find increased odds of falls in groups with less opportunity to develop tolerance (i.e., the restart and intermittent groups). However, these findings were not consistently significant in analyses in cohorts limited to new users of opioid therapy, or analysis limited to resident with high probability of group membership.

Fall odds were similar in the extended high and short-term groups, despite no exposure to opioids in the 150-days prior to fall assessment in the short-term group. This could suggest that tolerance to opioid-related sedation does develop in LTC residents receiving consistent high dose (around 90 MEDD) opioid therapy. Meanwhile, the proximity of opioid exposure to the follow-up period and fluctuations in dosing could be putting residents receiving intermittent and restart opioid dosing patterns at increased risk of falls. [68,79] A recent nested case-control study of non-cancer chronic pain patients prescribed long-term opioid therapy found that the risks of opioid overdose were attenuated (by 30.8%) when dose variability was included in the analysis.[100] This suggests that how opioid dose changes over time could confound that association between opioid use and opioid-related safety risks.

A lack of consistent findings from stratified analyses could suggest that opioid tolerance development does not play a significant role in opioid-related sedation. Previous study on the interaction between age and opioid tolerance suggest age-related changes in opioid receptors might hinder tolerance development. Studies in neuronal cells and in rats suggest that down regulation of opioid receptors, age-related changed to N-

methyl-D-aspartic acid (NMDA) receptors and other age related changes to opioid signaling pathways might diminish aged person's ability to develop opioid tolerance.[78] While sparce, a few observational studies assessing potential effects of changes in opioid dosing support the theory of age's interaction with tolerance development. One small study of 66 nursing home residents found that opioid treatment interruptions, defined as dose reductions as greater than 50% for at least one day resulted in no withdrawal symptoms.[68] Another study of 206 patients suffering from chronic pain found that older patients, regardless of sex or type of pain, were significantly less likely to require opioid dose escalations, as indicated by increasing pain, over a two year period.[101]

Previous studies accessing fall-risks in older adults and nursing home residents use summary measures of opioid use focused on dose and duration over a set period. These studies have found increased risk of fall at doses above 50 MEDD. One study assessing central nervous system medication burden in older nursing home residents, found an 83% increase in odds of serious falls among residents receiving three-times the standardized daily dose burden of centrally sedating medications (equivalent to about 30 MEDD) compared to those with no exposure.[44] Another study of 2,341 adults over the age of 60 with chronic non-cancer pain found a two-fold increase in fracture risk among those receiving ≥ 50MEDD compared to those with no exposure.[90] Our study found no difference in falls between groups of residents using average MEDDs over 80 and those without any acute exposure to opioids for at least 150-days prior to the event. This might suggest that dose alone does not predict fall-risk. A more nuanced approach to opioid safety assessments that incorporates prior patterns of opioid use might be warranted.

This study has several limitations. To ensure we would be able to describe opioid exposure and fall throughout the study, we required all residents be followed for 360 days. Sicker residents with hospitalizations or death were excluded. We chose to run analyses in this possibly healthier subset of LTC residents to reduce the high degree of bias that missing data cause in LCGM.[73] Still, this decision does limit the generalizability of our findings; further research on the patterns of opioid use over time are needed to quantify the degree to which selection bias is affecting our analysis. Like all claims-based analyses, we assumed opioids were used as prescribed. Relative to their community counterparts, prescriptions probably better reflect medication use in nursing home residents where medication use is managed by facility staff rather than residents. Still, it is possible that titration schedules or patient refusal led to opioid use patterns not discernable from claims. Also, we likely underestimated opioid use prior to nursing home admission as we were not able to identify hospitalization-related opioid use. Our look-back period to identify prior opioid use of 30 days was longer than the national average for hospitalization stay-length (about five days)[80] and therefore likely captured prior opioid use outside of the hospital. While we did control for characteristics that might impact fall risk and opioid use, it is still possible that we did not identify important confounders that might bias results. Other medications that cause falls, increasing morbidity, and worsening pain could lead to changes in opioid therapy and falls. Future research should examine specific reasons for dose changes and how that may impact safety-risks. Lastly, the patterns of opioid dose over time identified from our cohort are population averages and heterogeneity within each class was not investigated. Studies in

larger cohorts of LTC residents might be able to identify additional patterns of opioid dosing over time.

The study also has several strengths. We are the first to use a person-centered novel method to identify opioid dose patterns over time in LTC residents. Understanding that both claims, and fall-reports underestimate falls in nursing home resident,[98] we used a validated algorithm for identifying fall-related injuries from claims and reports of fall in the MDS to maximize our capture of fall events. We used facility clustered generalized estimating equations to account for correlation between residents in the same facility. Finally, we did not limit our study to certain opioid products; we included combination and non-oral formulations.

## Conclusion

There are four common patterns of opioid dose over time among LTC Medicare beneficiaries; short-term, intermittent, restart and extended high. This study suggests that dosing pattern over time might moderate fall-risks associated with high dose opioid therapy. Additional studies accessing the magnitude by which opioids-related safety risks are attenuated or exacerbated by varying opioid dosing strategies in LTC nursing home residents are needed.

## CHAPTER 4: DISCUSSION

### Final Summary and Significance

The objective of the proposed research was to build upon our understanding of how opioids are initially used in long-term care Medicare (LTC) residents with non-malignant pain, and how this use is associated with opioid-related safety outcomes. The analysis, guided by Andersen's Behavioral Model of Health Services Use, used Generalized Estimating Equations, multinomial regression, and latent class growth modeling to answer the following multilevel questions:

Aim 1) How has opioid use in the nursing home been changing over time?

- Are doses, durations, and frequency of opioid therapy changing?
- Does the change vary across commonly served nursing home populations (i.e., dementia, hospice, non-cancer chronic pain, and cancer)?
- Are pain-adjuvant opioid combinations being used more frequently?

Aim 2) How are opioid's dosed over time (180-days) in the nursing home?

- Are there different patterns of dose?
- In whom do these varying patterns occur?

3) Do varying patterns of opioid dose over time cause more falls? `

### Aim 1: Opioid and Opioid-Pain Adjuvant Combination Use Among Cancer-, Hospice-, Chronic Pain-, and Dementia-Related Long-Term Care Stays, 2011-2015.

In aim 1, we conducted a repeat cross-sectional study using 2011 to 2015 Medicare claims, survey data, and facility data to examine patterns of opioid use alone and in conjunction with pain-adjuvant medications among general, hospice, cancer, non-cancer chronic pain and dementia-related LTC stays. We hypothesized guidelines and a continued need for pain management would lead to decreasing trends in opioid use and

increasing trends in use of other pain adjuvant medications. We used opioid and pain-adjuvant (i.e., select antidepressants, anticonvulsants, skeletal muscle relaxants, and steroids) prescriptions from Medicare part D claims over the entire stay to identify any, high dose (>90 morphine milligram equivalents daily), long-term (>90days), high saturation (therapy over at least >50% of stay) opioid therapy, as well as opioid pain-adjuvant therapy. Opioid pain-adjuvant combinations were defined as opioid-related stays that had any pain-adjuvant medication use. Resident and facility adjusted logistic regression models with generalized estimating equations (GEE) with sandwich estimators and fixed year effects quantified annual changes while accounting for correlation between multiple stays from a single resident.

From 2011 to 2015, analysis adjusted by facility and resident characteristics found no constant significant changes in dose, duration, or frequency of opioid use in any LTC stay group studied. Relative to other studied groups, cancer-related LTC stays had the highest prevalence of any, high dose, and high saturation opioid use and dementia-related stays had the lowest prevalence of any or high dose opioid therapy. Use of skeletal muscle-relaxants and anticonvulsants during opioid-related stays increased from 2011 to 2015 across all studied LTC groups. Relative to 2011, odds of opioid related LTC dementia stays with anticonvulsants and skeletal muscle relaxants increased by 33% and 116% in 2015, respectively.

The findings from this work expanded on previous studies to provide a better understanding in whom and to what extent opioids alone and in conjunction with pain-adjuvant medications are used in long-term care nursing homes. A previous study on opioid use suggested guidelines and concerns stemming from the opioid epidemic in

younger community dwelling populations might be impacting opioid use in the long-term care setting.[17] Our analysis of opioid use over the entire nursing home stay failed to confirm this trend. The high prevalence of pain and painful comorbidities[6,10–12,102,103], the risks of undertreated pain[31–33,102], and limited alternative treatment options[4] might warrant long-term or high dose opioid use. While long-term and high dose opioid use among older adults in the community have been linked to overdose and death,[1,69,100,104] opioid overdose might not pertain to populations where medication administration is done by medical professionals.

We did identify sharp increases in the use of anticonvulsant and skeletal muscle relaxants in opioid-related stays, particularly among residents with dementia. Similar increases in anticonvulsant use with opioids have been found among older adults with opioid overdose and opioid abuse diagnoses.[105] While policies by the Centers for Medicare and Medicaid Services (e.g., the National Partnership to Improve Dementia Care in Nursing Homes) aimed to reduce the use of contraindicated psychopharmacological medications,[106] our findings suggest that issues of high psychopharmacologic use continue to be a major concern in this care setting and among residents with dementia. Studies evaluating safety risks with administration of anticonvulsants and skeletal muscle relaxants have found increased risks of overdose, cognitive impairment, falls, and hospitalizations.[3,43,62–65,75,104,105,107] Given the potential association with safety-risks and the evidence of increasing trends in use, more focus and research on the implications and risks associated with specific pain-adjuvant opioid combinations among the various LTC population served in nursing home facilities are needed.

Aim 2: Changes in Opioid Dose Over Time Among Long-Term Care Nursing Home residents: A Latent Class Growth Modeling Analysis.

In aim 2, we used latent class growth modeling (LCGM) to identify common patterns of opioid dosing over time used in long-term care residents. While we were not sure what the patterns would look like, we hypothesized that we would identify multiple distinct dosing patterns. We expected that these distinct groups to be highly associated with resident factors already identified in previous literature as associated with receipt of pain treatment and safety-related risks (e.g., cognitive function, use of other medications, psychiatric disorders, and pain-related diagnoses). Average morphine equivalent daily dose (MEDD) across six 30-day intervals starting with the first opioid prescription were identified from Medicare part D claims for 12,605 long-term care Medicare beneficiaries with non-malignant pain and opioid use from 2011 to 2015. Multivariate multinomial regression was used to quantify associations between different opioid use patterns over time and clinical and demographic resident characteristics.

Four patterns were identified; extended high, short-term, intermittent and restart. Patterns varied in average MEDDs, duration, magnitude of dose changes and direction of dose changes over time. Almost half of LTC residents received extended high opioid dosing. On average, the extended high dose group received average MEDDs between 80.7 and 98.0 for 75.6 days over a 180-days period. Short-term therapy was found in 26.9% of LTC residents and was characterized by 9 days of therapy, average MEDDs of 45.3, and no opioid exposure after the first 30-day interval. Intermittent therapy was found in 14.9% of LTC residents and consisted of increasing then decreasing MEDDs (minimum average MEDD=9.7 and maximum average MEDD=63.2 over 150-days) with

19.5 opioid-days over 150-days. Restart therapy was characterized by 75.6 opioid-days over 180-days with moderate to high MEDDs in the first, fifth and last 30-day interval and low MEDDs in the 2nd, 3rd, and 4th 30-day intervals. Multinomial regression found significant associations between receipt of extended high dose therapy and non-Hispanic black race, female sex, intact cognition, anxiety, manic depression, prior opioid use, chronic-non-cancer pain, and other pain treatments (including non-pharmacological therapies as well as pain-adjuvant antidepressant, anticonvulsant, and skeletal muscle-relaxant therapies).

Using a novel person-centered method, we identified four distinct patterns of opioid dose over time. Opioid dose changes over time, likely due to progression of disease and episodes of acute illness common among nursing home residents,[68] could result in varying opioid-related safety risks. A recent nested cohort study among privately insured patients in Colorado with chronic pain found that regardless of average daily opioid dose, the changes in dose over a 120 day period were associated with increased risk of opioid overdose.[100] Relative to their community counterparts, the risk associated with dose changes could be greater in the older, frailer, multimorbid LTC resident population. Or they could be attenuated in LTC where day-to-day therapy management and resident monitoring could allow staff to reduce risks and quickly mitigate adverse drug events. Prediction of risks associated with varying opioid dosing over time patterns using previous studies with definitions for long-term (>90 days) and high dose (>50 MEDD) opioid therapy are difficult. [95,103] For example, during the 180-day follow-up, most residents had opioid use around or above 50 MEDD at some point. If changes in opioid dosing over time are a factor in predicting opioid-safety risks, previous estimates

that do not consider changes over time might be over or under-estimating the impact opioids have on that outcome. Given the variation of opioid dosing patterns over time, more research on the safety impacts associated with changes in opioid dosing over the course of therapy are needed.

Also highlighted in this research were demographic and clinical characteristics associated with different opioid dosing patterns. Relative to residents receiving short-term therapy, a higher prevalence in extended high therapy residents with pain-related treatments and conditions suggest that residents receiving high extended therapy are those who have chronic pain sequalae that is being recognized and treated by the facility. Demographic and other clinical differences, however, might suggest inequities in dosing strategies rather than differences in pain duration and severity. Female sex, psychiatric disorders, and a lack of cognitive impairment have consistently been associated with increased risk of varying patterns of opioid use including any, high dose, long-term, and long-acting opioid therapy. [6,10,17,31–34,108] The co-occurrence of chronic pain conditions and psychiatric conditions, such as anxiety and manic depression, have long been established;[51] a higher likelihood of extended high versus short-term therapy in individuals with psychiatric conditions is not unexpected. Sex-based differences in the perception, expression, and behavioral response to pain and pain treatments could be why female residents are more likely to receive extended high opioid therapies.[109] Diminished pain expression ability[10,34] could also serve to explain why cognitively impaired adults were likely to receive extended high dosing versus short-term dosing strategies. Non-Hispanic Black race had strong associations with receipt of extended high dose therapy. Previous work on accessing any, high dose, or long-term, or long-acting opioid use have

found Black race to be protective.[16,17] Further research on the motivations behind how and why clinicians choose to provide opioid therapy for pain are needed to ensure clinical expression rather than bias motivate clinical decisions.

Aim 3: Opioid dosing over time and falls among long-term care nursing home residents: a latent class analysis.

Aim 3 built upon work from aim 2 by accessing the odds of falls among residents with the highest probability of belonging to each of the commonly identified opioid dosing patterns. Specifically, we followed a cohort of over 10,000 LTC residents for at least one year and used facility-clustered generalized estimated equations adjusted by resident demographic and clinical characteristics to compare odds of falls across varying opioid dose over time patterns. We compared residents who received short-term, intermittent, and restart therapy to the extended high group. We hypothesized that we would find similar odds of fall in the short-term group and the extended high group because tolerance to opioid-related sedation was likely in the extended high group. We also expected to see increased odds in falls among dynamic dosing patterns with a lower likelihood of tolerance development (i.e., intermittent and restart therapy).

Fall odds were found to be similar in the extended high and short-term groups, despite no exposure to opioids in the 150-days prior to fall assessment in the short-term group. Models did find increased odds of falls in groups with less opportunity to develop tolerance (i.e., the restart and intermittent groups). However, these findings were not consistently significant in analyses in cohorts limited to new users of opioid therapy, or analysis limited to resident with high probability of group membership.

Our findings indicate that more nuanced measures of opioid use might be necessary to better identify groups of LTC residents with increased opioid-related safety risks. We found no difference in falls between residents receiving consistent MEDDs over 80 and those without any acute exposure to opioids for 150-days. Difference in study design and population might explain why findings differ. Another explanation could be that opioid dosing patterns over time modify dose-related risks. As noted previously, high dose long-term opioid strategies might be warranted in LTC residents.[4,6,10–12,30–33,56,102,103] Previous work in opioid-related safety have found increased risk of serious falls and fractures at doses less than 50 MEDDs in older adults.[95,103] If patterns of opioid dosing do modify dose-related risks, guidelines and quality metrics based on only dose could serve to unnecessarily hinder opioid therapy access in nursing homes. Further research on the role of opioid dose patterns over time and how that interacts with dosage and duration thresholds and opioid-related safety risks are warranted.

Strengths

Our study used multiple data sources to aid in assessment of several resident characteristics. In calculating average morphine milligram equivalents, we include all opioid products, including combination and non-oral formulations. We also identified our cohort of LTC residents using a validated algorithm that incorporated both the MDS and Medicare part A claims.[47] We also identified common pain conditions associated with opioid therapy using both claims and MDS assessments were identified to see what conditions likely lead to opioid use.[50,51]

In aim 1, we improved upon previous literature describing opioid use in LTC residents by expanding our study period to include the entire LTC stay and describing the

use of concurrent opioid and MR medications. We also accounted for increased risk of opioid exposure with increasing length of LTC stay by creating an opioid-use saturation measure describing the proportion of days during a stay in which opioids were supplied.

In aims 2 and 3, we used a novel person-centered analysis strategy to identify different opioid dose patterns over time in the nursing home population. We used an enhanced race measure with positive predictive values of 98.7%, 95.9%, and 84.8% for identifying Non-Hispanic White, Non-Hispanic Black, and Hispanic races, respectively.[110] We identified pain adjuvant medication, PRN pain, and non-pharmacological pain treatment use to provide a comprehensive understanding of how LTC resident's pain is treated.

Limitations

This work is not without limitations. All analysis used data from 2011 to 2015, which may be during a unique period for opioid use. Since 2015, prescription drug policies at the federal level, emerging guidelines on opioid treatment, and nursing home quality metrics have emerged and could limit the generalizability of our findings to current LTC populations. Recent changes include scheduling changes for long-acting opioids, the emergence of prescription drug monitoring programs, the release of CDC's guidelines for opioid treatment in chronic pain, efforts to reduce antipsychotic prescribing in nursing homes, and the 2017 mandating of opioid medication use reporting in MDS.[1,4,106,111] As these guidelines and policies take effect, continuous efforts to describe and disseminate how opioids are used in the LTC population are necessary to ensure policy and guidelines adequately address pain management need while ensuring access to opioid therapy when necessary.

As with all Medicare Part D claims-based analyses, we were unable to identify indications for medication use and could not evaluate the use of over-the-counter medications. Inpatient claims, outpatient claims, and MDS assessments were used to identify conditions often associated with opioid therapy, and to identify residents receiving any scheduled or PRN pain medication therapy (which could include over the counter medications). Additional research linking indications to prescriptions and providing reliable information on over-the counter medication use is needed to provide a complete picture of pain management in this population.

Like all claims-based analyses, we also assumed opioids were used as prescribed. Relative to their community counterparts, prescriptions probably better reflect medication use in nursing home residents where medication use is managed by facility staff rather than residents. Still, it is possible that titration schedules or patient refusal led to opioid use patterns not discernable from claims.

While we did include several resident and facility characteristics that may impact opioid therapy and fall-risk, it is still likely that unmeasured confounders resulted in characteristics in our population that biased our results. For example, residents who receive pain adjuvants in addition to their opioid therapy likely have more severe pain then those who do not. While severity of pain is available in the MDS, the variable was missing for over 76% of the sample in aim 1 and 57% of our sample in aims 2 and 3, thereby precluding use of this measure. Likewise, residents who receive extended high dose therapy are likely less frail and less likely to experience falls relative to individuals whose therapy was reduced or discontinued. While we are unaware of any validated measures of frailty in this population, we know that this is an emerging field of

research.[112,113] Future studies using a measure for frailty could better control for variations in the robustness of residents seen in LTC.

In aim 1, opioid and pain adjuvant medication use may have been underestimated among hospice-related stays.[67] Medicare provides a set daily reimbursement rate for individuals receiving hospice that includes medications; thus, use of medications, including opioids, are not discernable from claims. Other future studies using different data sources could ensure full capture of prescription medications among hospice patients. Also, in aim 1 our reliance on self-report of dementia diagnoses could have led to under-reporting of this diagnosis. Report of dementia diagnosis on MDS 3.0 might serve as a better indicator of the facilities awareness of a diagnosis.

In aims 2 and aim 3, we required all residents be followed for at least 180 or 360 days. Sicker residents with hospitalizations or death were excluded. We chose to run analyses in this possibly healthier subset of LTC residents to reduce the high degree of bias that missing data cause in LCGM. Further research on the patterns of opioid use over time are needed to quantify the degree to which selection bias is affecting our analysis. Also, we likely underestimated opioid use prior to nursing home admission as we were not able to identify hospitalization-related opioid use. Our look-back period to identify prior opioid use of 30 days was longer than the national average for hospitalization stay-length (about five days)[80] and therefore likely captured prior opioid use outside of the hospital. Falls are under-reported in MDS and claims.[97,98] To compensate for this, we used MDS assessments and inpatient and emergency room visit claims to identify residents who fell. Still, research using a more robust measure of falls are needed to confirm our analysis. Lastly, the latent class growth modeling classified the participants

into heterogenous groups based on the growth of opioid use over time. We did not account for the variation in the growth within each class.

Future directions

Use of opioid therapy in conjunction with other pain adjuvants is increasing in LTC residents, particularly in residents with dementia. Literature supporting multimodal pain management, or the use of multiple analgesic agents and techniques that act on different pain mechanisms, are increasing.[60,114–116] Studies focused on post-operative populations have found associations between multimodal pain management (which often includes opioids) and decreased opioid use, as well as less opioid-related sedation, nausea, vomiting, itching, and respiratory depression.[114] However, the benefits of such practices in the LTC setting remain unclear. On the one hand, the benefits seen in the postoperative population are appealing and might be applicable in a population that often transitions from hospital to nursing home after a surgical event. On the other, literature evaluating the use of multiple centrally acting medications find increased safety-risks.[3,43,117] Moreover, while there is a good deal of literature on the factors associated with falls and fractures in nursing home residents,[20,24,44,63,64,71,93,95,117–121] analyses of opioid use and its association with other outcomes relevant to this population remain scant. More research on the safety-risks associated with specific medication combinations and LTC relevant safety outcomes, such as falls, cognitive impairment and hospitalizations, are needed to better understand how and with what opioids and pain adjuvant combinations we can meet resident's needs while minimizing opioid-related safety risks.

Research on the safety implications associated with opioid dosing patterns with consideration of other use patterns associated with opioid-related safety risks are also needed. Opioid dose, duration, duration of action, formulation, the use of add on pain pharmacologic therapies, and how an opioid is used over time might all serve as factors in predicting opioid-related safety. Policies and guidelines that do not consider all these factors could lead to unintended harms. For example, guidelines focused on opioid dose and duration prompted Medicare to add requirements for prior authorization and dose and duration limits of prescribed opioids in 2019.[122] Within a few months of the policy, increasing reports of patient destabilization, severe withdrawal, patient suffering, and disability after abrupt cessation or rapid tapers of opioid therapy prompted the U.S. Food and Drug administration to release a warning against rapid tapers or abrupt cessation of opioids.[122,123] In LTC pain is common and opioid use might be warranted. Research that considers all potential opioid-related safety factors would lead to more precise identification of high-risk groups leaving residents who benefit from therapy free to continue receiving those benefits.

Finally, we would like to end this dissertation with a call for more inclusion of the resident's perspective in research, guidelines, and clinical decision making. Although a considerable literature exists that provides insights from nursing home clinicians, nurses, and caregivers,[124–128] a major gap remains in capturing the patient's voice regarding their pain. Guidelines concerning pain management of older adults and long-term care residents[22] are void of resident input beyond assessments of the severity and responsiveness of pain to pharmacological therapy. Particularly with opioid pain treatment, a better understanding of pain tolerance and opioid side-effect preferences are

needed to guide research and guideline development for LTC residents. While barriers to conducting qualitative research in nursing home facilities do exist,[129] redoubled efforts to conduct this research is needed to ensure research best serves resident needs.

## REFERENCES


1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States, 2016. *JAMA - J Am Med Assoc*. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464

2. Ickowicz E. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331-1346. doi:10.1111/j.1532-5415.2009.02376.x

3. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694. doi:10.1111/jgs.15767

4. Edelman LS, Hemmert R. Opioid Use in Long-Term Care: Guidelines and Policy Recommendations. *J Gerontol Nurs*. 2019;45(9):5-10. doi:10.3928/00989134-20190813-02

5. Lapane KL, Quilliam BJ, Chow W, Kim M. The Association Between Pain and Measures of Well-Being Among Nursing Home Residents. *J Am Med Dir Assoc*. 2012;13(4):344-349. doi:10.1016/j.jamda.2011.01.007

6. Hunnicutt JN, Ulbricht CM, Tjia J, Lapane KL. Pain and pharmacologic pain management in long-stay nursing home residents. *Pain*. 2017;158(6):1091-1099. doi:10.1097/j.pain.0000000000000887

7. Goodwin JS, Li S, Graham JE, Karmarkar A, Ottenbacher K. Comparison of methods to identify long term care nursing home residence with administrative data. *BMC Health Serv Res*. 2017;17(1):1-9. doi:10.1186/s12913-017-2318-9

8. Wei YJ, Simoni-Wastila L, Zuckerman IH, Brandt N, Lucas JA. Algorithm for identifying nursing home days using medicare claims and minimum data set assessment data. *Med Care*. 2016;54(11):e73-e77. doi:10.1097/MLR.0000000000000109

9. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *Long-Term Care Providers and Services Users in the United States, 2015–2016 Analytical and Epidemiological Studies*. Vol 3.; 2019.

10. Fain KM, Alexander GC, Dore DD, Segal JB, Zullo AR, Castillo-Salgado C. Frequency and Predictors of Analgesic Prescribing in U.S. Nursing Home Residents with Persistent Pain. *J Am Geriatr Soc*. 2017;65(2):286-293. doi:10.1111/jgs.14512

11. Shen X, Zuckerman IH, Palmer JB, Stuart B. Trends in prevalence for moderate-to-severe pain and persistent pain among medicare beneficiaries in nursing homes, 2006-2009. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2015;70(5):598-603. doi:10.1093/gerona/glu226

12. Fain KM, Castillo-Salgado C, Dore DD, Segal JB, Zullo AR, Alexander GC. Inappropriate Fentanyl Prescribing Among Nursing Home Residents in the United States. *J Am Med Dir Assoc*. 2017;18(2):138-144. doi:10.1016/j.jamda.2016.08.015

13. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *J Pain Symptom Manage*. 2010;40(2):279-289. doi:10.1016/j.jpainsymman.2010.01.012

14. Jarrín OF, Nyandege AN, Grafova IB, Dong X, Lin H. Validity of Race and Ethnicity Codes in Medicare Administrative Data Compared with Gold-standard Self-reported Race Collected during Routine Home Health Care Visits. *Med Care*. 2020;58(1):E1-E8. doi:10.1097/MLR.0000000000001216

15. Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of Long-Term Opioid Use in Long-Stay Nursing Home Residents. *J Am Geriatr Soc*. 2018;66(1):48-55. doi:10.1111/jgs.15080

16. Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of Long-term Opioid Use in Long-Stay Nursing Home Residents. *JAGS*. 2018;66(1):48-55. doi:10.1111/jgs.15080

17. Mehta HB, Kuo YF, Raji M, Li S, Westra J, Goodwin JS. Time Trends in Opioid Use by Dementia Severity in Long-Term Care Nursing Home Residents. *J Am Med Dir Assoc*. 2021;22(1):124-131. doi:10.1016/j.jamda.2020.04.029

18. Field TS, J. A, McCormick D, et al. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med*. 2001;161(13):1629-1634. doi:10.1001/archinte.161.13.1629

19. Al-Jumaili AA, Doucette WR. Comprehensive Literature Review of Factors Influencing Medication Safety in Nursing Homes: Using a Systems Model. *JAMDA*. Published online 2017:470-488.

20. Wei Y-J, Simoni-Wastila L, Lucas JA, Brandt N. Fall and Fracture Risk in Nursing Home Residents With Moderate-to-Severe Behavioral Symptoms of Alzheimer's Disease and Related Dementias Initiating Antidepressants or Antipsychotics. *Journals Gerontol Ser A Biol Sci Med Sci*. 2016;72(5):glw095. doi:10.1093/gerona/glw095

21. Allen Carrie, Zarowitz Barbara J. OT, Datto Catherine OT. Clinical and Functional Characteristics of Nursing Facility residents with Opioid-Induces Constipation. *Consult Pharm*. 2017;32(5):754-763.

22. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: A clinical review. *JAMA - J Am Med Assoc*. 2014;312(8):825-836. doi:10.1001/jama.2014.9405

23. Aspinall SL, Springer SP, Zhao X, et al. Central Nervous System Medication Burden and Risk of Recurrent Serious Falls and Hip Fractures in Veterans Affairs Nursing Home Residentse. *JAGS*. 2019;67(1):74-80.

24. Hunnicutt JN, Hume AL, Liu SH, Ulbricht CM, Tjia J, Lapane KL. Commonly Initiated Opioids and Risk of Fracture Hospitalizations in United States Nursing Homes. *Drugs and Aging*. 2018;35(10):925-936. doi:10.1007/s40266-018-0583-x

25. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States, 2016. *JAMA - J Am Med Assoc*. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464

26. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. *Pain*. 2010;150(2):332-339. doi:10.1016/j.pain.2010.05.020

27. Ray WA, Chung CP, Murray KT, Hall K, Michael Stein C. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. *JAMA - J Am Med Assoc*. 2016;315(22):2415-2423. doi:10.1001/jama.2016.7789

28. AMDA. AMDA Clinical Practice guideline: Pain Management in ALFs. *Assist Living Consult*. Published online 2005:28-32.

29. Miller M, Stürmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc*. 2011;59(3):430-438. doi:10.1111/j.1532-5415.2011.03318.x

30. Smith TO, Purdy R, Latham SK, Kingsbury SR, Mulley G, Conaghan PG. The prevalence, impact and management of musculoskeletal disorders in older people living in care homes: a systematic review. *Rheumatol Int*. 2016;36(1):55-64. doi:10.1007/s00296-015-3322-1

31. Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. *J Am Geriatr Soc*. 2004;52(6):867-874. doi:10.1111/j.1532-5415.2004.52251.x

32. Noble M, Treadwell J, Tregear S, et al. Long-term opioid management for chronic noncancer pain (Cochrane Review). *Cochrane*. 2010;(11). doi:10.1002/14651858.CD006605.pub2.Copyright

33. Cadogan MP, Edelen MO, Lorenz KA, et al. The relationship of reported pain severity to perceived effect on function of nursing home residents. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2008;63(9):969-973. doi:10.1093/gerona/63.9.969

34. Monroe TB, Misra SK, Habermann RC, Dietrich MS, Cowan RL, Simmons SF.

Pain reports and pain medication treatment in nursing home residents with and without dementia. *Geriatr Gerontol Int*. 2013;14:541-548.

35. Glanz K, Rimer B, Viswanath K. Health Behavioral Model. In: *Health Behavior and Health Education*. ; 2008:45-62.

36. Hunnicutt JN, Ulbricht CM, Tjia J, Lapane KL. Pain and Pharmacologic Pain Management in Long-Stay Nursing Home Residents. *Pain*. 2017;158(6):1091-1099. doi:10.1097/j.pain.0000000000000887.

37. Shen X, Zuckerman IH, Palmer JB, Stuart B. Trends in prevalence for moderate-to-severe pain and persistent pain among medicare beneficiaries in nursing homes, 2006-2009. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2015;70(5):598-603. doi:10.1093/gerona/glu226

38. Quigley C. Opioids in people with cancer-related pain. *BMJ Clin Evid*. 2008;2008(July 2007):1-16.

39. Ickowicz E. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57(8):1331-1346. doi:10.1111/j.1532-5415.2009.02376.x

40. Fain KM, Alexander GC, Dore DD, Segal JB, Zullo AR, Castillo-Salgado C. Frequency and Predictors of Analgesic Prescribing in U.S. Nursing Home Residents with Persistent Pain. *J Am Geriatr Soc*. 2017;65(2):286-293. doi:10.1111/jgs.14512

41. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;2017(6). doi:10.1002/14651858.CD008943.pub2

42. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: From bench to bedside. *Lancet Neurol*. 2013;12(11):1084-1095. doi:10.1016/S1474-4422(13)70193-5

43. Wright RM, Roumani YF, Boudreau R, et al. Effect of central nervous system medication use on decline in cognition in community-dwelling older adults: Findings from the health, aging and body composition study. *J Am Geriatr Soc*. 2009;57(2):243-250. doi:10.1111/j.1532-5415.2008.02127.x

44. Joseph T. Hanlon, Zhao X, Naples JG, et al. Central Nervous System Medication Burden and Serious Falls in Older Nursing Home Residents. *JAGS*. 2017;65(6):1183-1189. doi:10.1111/jgs.14759

45. Shaping Long Term Care in America Project at Brown University funded in part by the National Institute on Aging (1P01AG027296).

46. Wei Y-JP, Simoni-Wastila L, Zuckerman IH, Brandt N, Lucas J. Algorithm for Identifying Nursing Home Days Using Medicare Claims and Minimum Data Set

Assessment Data. *Med Care*. 2016;54(11):e73-e77. doi:10.1097/MLR.0000000000000109

47. Goodwin JS, Li S, Zhou J, Graham JE, Karmarkar A, Ottenbacher K. Comparison of methods to identify long term care nursing home residence with administrative data. *BMC Health Serv Res*. 2017;17(1):1-8. doi:10.1186/s12913-017-2318-9

48. Intrator O, Hiris J, Berg K, Miller SC, Mor V. The residential history file: Studying nursing home residents' long-term care histories. *Health Serv Res*. 2011;46(1 PART 1):120-137. doi:10.1111/j.1475-6773.2010.01194.x

49. CMS. Condition Categories. Published 2015. Accessed May 8, 2020. https://www2.ccwdata.org/web/guest/condition-categories

50. Owen-Smith A, Stewart C, Sesay MM, et al. Chronic pain diagnoses and opioid dispensings among insured individuals with serious mental illness. *BMC Psychiatry*. 2020;20(1):1-10. doi:10.1186/s12888-020-2456-1

51. Edlund MJ, Martin BC, Devries A, Fan MY, Brennan Braden J, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: The TROUP study. *Clin J Pain*. 2010;26(1):1-8. doi:10.1097/AJP.0b013e3181b99f35

52. Hunnicutt JN, Baek J, Alcusky M, et al. Geographic variation in the initiation of commonly used opioids and dosage strength in United States nursing homes. *Med Care*. 2018;56(10):847-854. doi:10.1097/MLR.0000000000000972

53. Leslie R. Using Arrays to Calculate Medication Utilization. *SAS Glob Forum*. Published online 2007:1-5.

54. CMS. Opioid Oral Morphine Milligram Equivalent ( MME ) Conversion Factors. *Centers Medicaire Medicaid Serv*. Published online 2018:2.

55. Stokes A, Berry KM, Hempstead K, Lundberg DJ, Neogi T. Trends in Prescription Analgesic Use Among Adults With Musculoskeletal Conditions in the United States, 1999-2016. *JAMA Netw open*. 2019;2(12):e1917228. doi:10.1001/jamanetworkopen.2019.17228

56. Monroe TB, Carter MA, Feldt KS, Dietrich MS, Cowan RL. Pain and hospice care in nursing home residents with dementia and terminal cancer. 2016;13(4):1018-1025. doi:10.1111/ggi.12049.Pain

57. Liu S-H, Hunnicutt JN, Ulbricht CM, Dubé CE, Hume AL, Lapane KL. Adjuvant Use and the Intensification of Pharmacologic Management for Pain in Nursing Home Residents with Cancer: Data from a US National Database. *Drugs Aging*. 2019;36(6):549-557. doi:10.1007/s40266-019-00650-3.Adjuvant

58. Al-jumaili AA, Pharm BS, Doucette WR. PROGRAM DISSEMINATION A

Systems Approach to Identify Factors Influencing Adverse Drug Events in Nursing Homes. Published online 2018:1420-1427. doi:10.1111/jgs.15389

59. Hubert PJ. The behavior of maximum likelihood estimates under nonstandard conditions. In: Volume 1: University of California Press; 1967:221-233.

60. U.S. Department of Health and Human Services. *Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations*.; 2019.

61. Organization WHO and WH. *Cancer Pain Relief: With a Guide to Opioid Availability.*; 1996.

62. Weston AL, Weinstein AM, Barton C, Yaffe K. Potentially inappropriate medication use in older adults with mild cognitive impairment. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2010;65 A(3):318-321. doi:10.1093/gerona/glp158

63. Alvarez CA, Mortensen EM, Makris UE, et al. Association of skeletal muscle relaxers and antihistamines on mortality, hospitalizations, and emergency department visits in elderly patients: A nationwide retrospective cohort study. *BMC Geriatr*. 2015;15(1):1-8. doi:10.1186/1471-2318-15-2

64. Spence MM, Shin PJ, Lee EA, Gibbs NE. Risk of injury associated with skeletal muscle relaxant use in older adults. *Ann Pharmacother*. 2013;47(7-8):993-998. doi:0.1345/aph.1R735

65. Tannenbaum C, Paquette A, Hilmer S, Holroyd-Leduc J, Carnahan R. Re: A Systematic Review of Amnestic and Non-Amnestic Mild Cognitive Impairment Induced by Anticholinergic, Antihistamine, GABAergic and Opioid Drugs. *Drugs Aging*. 2012;29(8):639-658. doi:10.1016/j.juro.2013.08.105

66. Mehrpouya M, Ataei S, Nili-Ahmadabadi A. Potential drug interactions with cholinesterase inhibitors in alzheimer patients: A guideline for neurologists. *J Appl Pharm Sci*. 2017;7(1):223-226. doi:10.7324/JAPS.2017.70134

67. Medpac. *HOSPICE SERVICES PAYMENT SYSTEM*.; 2019.

68. Redding SE, Liu S, Hung WW, Boockvar KS. Opioid interruptions, pain, and withdrawal symptoms in nursing home residents. *Clin Ther*. 2014;36(11):1555-1563. doi:10.1016/j.clinthera.2014.10.013

69. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a national institutes of health pathways to prevention workshop. *Ann Intern Med*. 2015;162(4):276-286. doi:10.7326/M14-2559

70. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*.

2011;12(2):288-296. doi:10.1016/j.jpain.2010.09.003

71. Morasco BJ, Smith N, Dobscha SK, Deyo RA, Hyde S, Yarborough BJH. Outcomes of prescription opioid dose escalation for chronic pain: results from a prospective cohort study. *Pain*. 2020;161(6):1332-1340. doi:10.1097/j.pain.0000000000001817

72. Hayes CJ, Krebs EE, Hudson T, Brown J, Li C, Martin BC. Impact of opioid dose escalation on pain intensity: a retrospective cohort study. *Pain*. 2020;161(5):979-988. doi:10.1097/j.pain.0000000000001784

73. Thompson A, Gaudreau P, Louvet B, Andruff H, Carraro N. Latent Class Growth Modelling: A Tutorial. *Tutor Quant Methods Psychol*. 2016;5(1):11-24. doi:10.20982/tqmp.05.1.p011

74. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. *J Am Geriatr Soc*. 2010;58(9):1664-1670. doi:10.1111/j.1532-5415.2010.03015.x

75. Hanlon JT, Zhao X, Naples JG, et al. Central Nervous System Medication Burden and Serious Falls in Older Nursing Home Residents. *J Am Geriatr Soc*. 2017;65(6):1183-1189. doi:10.1111/jgs.14759

76. Hunnicutt JN, Hume AL, Liu S-H, Ulbricht CM, Tjia J. Commonly Initiated Opioids and Risk of Fracture Hospitalizations in United States Nursing Homes. *Drugs Aging*. 2018;35(10):925-936. doi:10.1007/s40266-018-0583-x.Commonly

77. Field TS, Gurwitz JH, Avorn J, et al. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med*. 2001;161(13):1629-1634. doi:10.1001/archinte.161.13.1629

78. Zhao J, Xin X, Xie G xi, Palmer PP, Huang Y guang. Molecular and cellular mechanisms of the age-dependency of opioid analgesia and tolerance. *Mol Pain*. 2012;8(1):1. doi:10.1186/1744-8069-8-38

79. Freye E, Latasch L. [Development of opioid tolerance -- molecular mechanisms and clinical consequences]. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 2003;38(1):14-26.

80. Freeman WJ, Weiss AJ, Heslin KC. Overview of U.S. Hospital Stays in 2016: Variation by Geographic Region. Agency for Health Research and Quality (AHRQ). Published 2018. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb246-Geographic-Variation-Hospital-Stays.jsp

81. Saliba D, Buchanan J, Edelen MO, et al. MDS 3.0: Brief Interview for Mental Status. *J Am Med Dir Assoc*. 2012;13(7):611-617. doi:10.1016/j.jamda.2012.06.004

82. Downer B, Thomas KS, Mor V, Goodwin JS, Ottenbacher KJ. Cognitive Status of Older Adults on Admission to a Skilled Nursing Facility According to a Hospital Discharge Diagnosis of Dementia. *J Am Med Dir Assoc*. 2017;18(8):726-728. doi:10.1016/j.jamda.2017.04.021.Cognitive

83. Thomas KS, Dosa D, Wysock A, Mo V. The Minimum Data Set 3.0 Cognitive Function Scale. *Med Care*. 2017;55(9):e68-e72. doi:10.1097/MLR.0000000000000334.The

84. Won AB, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. *J Am Geriatr Soc*. 2004;52(6):867-874. doi:10.1111/j.1532-5415.2004.52251.x

85. Inouye, S. K., van Dyck CH, Alessi CA, Balkin, S., Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method: a new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948.

86. Dosa D, Intrator O, McNicoll L, Cang Y, Teno J. Preliminary derivation of a nursing home confusion assessment method based on data from the minimum data set. *JAGS*. 2007;55(7):1099-1105.

87. Jung T, Wickrama KAS. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Soc Personal Psychol Compass*. 2008;2(1):302-317. doi:10.1111/j.1751-9004.2007.00054.x

88. Jones B. traj: group based modeling of longitudinal data.

89. Hunnicutt1 JN, Hume AL, Liu S-H, Ulbricht CM, Tjia1 J, Lapane KL. Commonly Initiated Opioids and Risk of Fracture Hospitalizations in United States Nursing Homes. *Drugs and Aging*. 2018;35(10):925-936. doi:10.1007/s40266-018-0583-x.Commonly

90. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med*. 2010;25(4):310-315. doi:10.1007/s11606-009-1218-z

91. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Am Coll physicians*. 2014;(160):38-47.

92. Vlaeyen E, Coussement J, Leysens G, et al. Characteristics and effectiveness of fall prevention programs in nursing homes: A systematic review and meta-analysis of randomized controlled trials. *J Am Geriatr Soc*. 2015;63(2):211-221. doi:10.1111/jgs.13254

93. Rubenstein LZ. Falls in older people: Epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(SUPPL.2):37-41. doi:10.1093/ageing/afl084

94. Bohl AA, Fishman PA, Ciol MA, Williams B, Logerfo J, Phelan EA. A longitudinal analysis of total 3-year healthcare costs for older adults who experience a fall requiring medical care. *J Am Geriatr Soc*. 2010;58(5):853-860. doi:10.1111/j.1532-5415.2010.02816.x

95. Yoshikawa A, Ramirez G, Smith ML, et al. Opioid use and the risk of falls, fall injuries and fractures among older adults: A systematic review and meta-analysis. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2020;75(10):1989-1995. doi:10.1093/gerona/glaa038

96. AGS. American Geriatric Society 2015 Updates Beers Criteria for potentially inappropriate medication use in older adults. *Am Geriatr Soc*. 2015;(63):2227-2246.

97. Sanghavi P, Pan S, Caudry D. Assessment of nursing home reporting of major injury falls for quality measurement on nursing home compare. *Health Serv Res*. 2020;55(2):201-210. doi:10.1111/1475-6773.13247

98. Min L, Tinetti M, Langa KM, Ha J, Alexander N, Hoffman GJ. Measurement of Fall Injury With Health Care System Data and Assessment of Inclusiveness and Validity of Measurement Models. *JAMA Netw open*. 2019;2(8):e199679. doi:10.1001/jamanetworkopen.2019.9679

99. Johnston G, Rodriguez RN. Introducing the HPGENSELECT Procedure : Model Selection for Generalized Linear Models and More. *Sgf2015*. Published online 2015:1-18.

100. Glanz JM, Binswanger IA, Shetterly SM, Narwaney KJ, Xu S. Association Between Opioid Dose Variability and Opioid Overdose Among Adults Prescribed Long-term Opioid Therapy. *JAMA Netw open*. 2019;2(4):e192613. doi:10.1001/jamanetworkopen.2019.2613

101. Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP. Age-dependent opioid escalation in chronic pain patients. *Anesth Analg*. 2005;100(6):1740-1745. doi:10.1213/01.ANE.0000152191.29311.9B

102. Lapane KL, Quilliam BJ, Chow W, Kim M. The Association Between Pain and Measures of Well-Being Among Nursing Home Residents. *J Am Med Dir Assoc*. 2012;13(4):344-349. doi:10.1016/j.jamda.2011.01.007

103. Hanlon JT, Perera S, Sevick MA, Rodriguez KL, Jaffe EJ. Pain and Its Treatment in Older Nursing Home Hospice/Palliative Care Residents. *J Am Med Dir Assoc*. 2010;11(8):579-583. doi:10.1016/j.jamda.2009.11.014

104. Rose AJ, McBain R, Schuler MS, et al. Effect of Age on Opioid Prescribing, Overdose, and Mortality in Massachusetts, 2011 to 2015. *J Am Geriatr Soc*. 2019;67(1):128-132. doi:10.1111/jgs.15659

105. Wei YJJ, Chen C, Schmidt SO, LoCiganic WH, Winterstein AG. Trends in prior receipt of prescription opioid or adjuvant analgesics among patients with incident opioid use disorder or opioid-related overdose from 2006 to 2016. *Drug Alcohol Depend*. 2019;204(July):107600. doi:10.1016/j.drugalcdep.2019.107600

106. National Partnership to Improve Dementia Care in Nursing Homes: Antipsychotic Medication Use Data Report. October 2020. Published 2020. https://www.cms.gov/files/document/antipsychotic-medication-use-data-report-2020q2-updated-01222021.pdf

107. Gomes T, Greaves S, Brink W van den, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case–Control. *Ann Intern Med*. 2018;169(10):732-737.

108. Hunnicutt JN, Hume AL, Ulbricht CM, Tjia J, Lapane KL. Long-acting opioid initiation in US nursing homes. *Pharmacoepidemiol Drug Saf*. 2018;(April 2018):31-38. doi:10.1002/pds.4568

109. Bartley EJ, Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. *Br J Anaesth*. 2013;111(1):52-58. doi:10.1093/bja/aet127

110. Zaslavsky AM, Ayanian JZ, Zaborski LB. The validity of race and ethnicity in enrollment data for medicare beneficiaries. *Health Serv Res*. 2012;47(3 PART 2):1300-1321. doi:10.1111/j.1475-6773.2012.01411.x

111. Moyo P, Simoni-Wastila L, Griffin BA, et al. Impact of prescription drug monitoring programs (PDMPs) on opioid utilization among Medicare beneficiaries in 10 US States. *Addiction*. 2017;112(10):1784-1796. doi:10.1111/add.13860

112. Parker DC, Colon-Emeric C, Huebner JL, et al. Biomarkers associated with physical resilience after hip fracture. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2020;75(10):E166-E172. doi:10.1093/gerona/glaa119

113. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: Systematic review and development of an emerging construct. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2016;71(4):489-495. doi:10.1093/gerona/glv202

114. Wick EC, Grant MC, Wu CL. Postoperativemultimodal analgesia pain management with nonopioid analgesics and techniques a review. *JAMA Surg*. 2017;152(7):691-697. doi:10.1001/jamasurg.2017.0898

115. Goode VM, Morgan B, Muckler VC, Jr. MPC, Zdeb CE, Zychowicz M. Multimodal Pain Management for Major Joint Replacement Surgery. *Othop Nurs*. 2019;38(2):150-156. doi:10.1097/NOR.0000000000000525.Multimodal

116. Brooks E, Freter SH, Bowles SK, Amirault D. Multimodal Pain Management in Older Elective Arthroplasty Patients. *Geriatr Orthop Surg Rehabil*. 2017;8(3):151-154. doi:10.1177/2151458517720297

117. Aspinall SL, Springer SP, Zhao X, et al. Central Nervous System Medication Burden and Risk of Recurrent Serious Falls and Hip Fractures in Veterans Affairs Nursing Home Residents. *J Am Geriatr Soc*. 2019;67(1):74-80. doi:10.1111/jgs.15603

118. Saraf A, Peterson AW, Simmons SF, et al. Medications Associated with Geriatric Syndromes (MAGS) and their Prevalence in Older Hospitalized Adults Discharged to Skilled Nursing Facilities. *J Hosp Med*. 2016;11(10):694-700. doi:10.1002/jhm.2614.Medications

119. Wolff ML, Kewley R, Collins J, Brodeur MiR, Nokes S. FALLS IN SKILLED NURSING FACILITIES ASSOCIATED WITH OPIOID USE. *JAGS*. 2012;60(5):987.

120. Cameron ID, Dyer SM, Panagoda CE, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev*. 2018;2018(9). doi:10.1002/14651858.CD005465.pub4

121. Spector W, Shaffer T, Potter DEB, Correa-De-Araujo R, Rhona Limcangco M. Risk factors associated with the occurrence of fractures in U.S. nursing homes: Resident and facility characteristics and prescription medications. *J Am Geriatr Soc*. 2007;55(3):327-333. doi:10.1111/j.1532-5415.2007.01081.x

122. Arnstein P, Herr K. From the Opioid Crisis to Quality Pain Management. *J Gerontol Nurs*. 2019;45(6):3-5.

123. Communication FDS. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. Published 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes

124. Cohen-Mansfield J, Creedon M. Nursing Staff Members' Perceptions of Pain Indicators in Persons With Severe Dementia. *Clin J Pain*. 2002;18:64-73.

125. Clark L, Jones K, Pennington K. Pain Assessment Practices With Nursing Home Residents. *West J Nurs Res*. 2004;24(733-750).

126. Jansen BDW, Brazil K, Passmore P, et al. Exploring healthcare assistants' role and experience in pain assessment and management for people with advanced dementia towards the end of life: a qualitative study. *BMC Palliat Care*. 2017;16(1):6. doi:10.1186/s12904-017-0184-1

127. Jennings AA, Linehan M, Foley T. The knowledge and attitudes of general practitioners to the assessment and management of pain in people with dementia. *BMC Fam Pract*. 2018;19(1):166. doi:10.1186/s12875-018-0853-z

128. Halifax E, Miaskowski C, Wallhagen M. Certified Nursing Assistants'

Understanding of Nursing Home Residents' Pain. *J Gerontol Nurs*. 2018;44(4):29-36. doi:10.3928/00989134-20180131-01

129. Lam HR, Chow S, Taylor K, et al. Challenges of conducting research in long-term care facilities: A systematic review. *BMC Geriatr*. 2018;18(1):1-11. doi:10.1186/s12877-018-0934-9