

**ASSESSING THE APPROPRIATENESS OF OPIOID PRESCRIBING  
IN ELDERLY NURSING HOME RESIDENTS**

by  
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**Abstract:**

Background: Untreated persistent pain causes much hardship for elderly nursing home residents. Analgesic prescribing can be critical to alleviate this pain, but inappropriate opioid prescribing can create serious health risks for residents.

Objectives: This dissertation examined the lack of analgesic prescribing for elderly nursing home residents in persistent pain, as well as opioid prescribing deviating from Food and Drug Administration (FDA) conditions, and identified those factors associated with no analgesic prescribing and inappropriate opioid prescribing.

Methods: Our study population is from a cross-section of all long-stay U.S. nursing home residents  $\geq 65$  years in 2008 with a Minimum Data Set assessment and Medicare Part D enrollment. Using these records, we quantified no analgesic prescribing for residents with persistent pain (aim one); inappropriate transdermal fentanyl initiation, i.e., without prior opioid use (“opioid-naïve”) or no persistent pain (aim two); and inappropriate oxycodone extended-release (ER) co-prescribing, i.e., with any central nervous system (CNS) depressant (aim three). We estimated associations of patient and facility attributes with these outcomes using multilevel mixed effects logistic regression analyses.

Results: We found 16.7% of residents with persistent pain did not receive a prescription analgesic (aim one); 36.3% of residents initiating transdermal fentanyl were opioid-naïve and 91.8% did not have persistent pain (aim two); and 26.6% of

residents were co-prescribed a CNS depressant with oxycodone ER (aim three).

Residents who were older or more cognitively impaired were less likely to receive a prescription analgesic (aim one); more likely to be opioid-naïve when initiating transdermal fentanyl (aim two); and less likely to be co-prescribed two or more CNS depressants with oxycodone ER (aim three).

Conclusion: Pain remains incompletely treated in U.S. nursing homes, especially among certain subpopulations, such as residents with greater cognitive impairment and older age. There are also substantial deviations in nursing homes from FDA conditions for safe use of long-acting opioids. FDA should take action to communicate these risks to nursing homes and ensure proper use, including through the long-acting opioid Risk Evaluation and Mitigation Strategy (REMS). Nursing homes should take steps to ensure appropriate long-acting opioid prescribing, particularly for residents without prior opioid use or persistent pain.

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## **Acknowledgements**

The seeds for this dissertation were planted decades ago, when my grandmother, Mary Fain, moved to the Wesley Woods assisted living facility in Atlanta, Georgia. During many visits there as an adolescent, I was struck by the unique aspects of this community in which my grandmother and her neighbors lived, whose basic needs were so fundamentally great. Since those days I have helped support other relatives in nursing homes, such as my other grandmother, Geneva Knight, and my great aunt, Margaree Gambill. My family struggled with decisions about their care, particularly because of their diminished capacity and suffering from pain. Some of the most difficult questions involved how best to alleviate this decline and anguish and improve their quality of life. Although pharmaceutical therapies were an important option, I also saw the dangers in nursing homes from inappropriate prescribing. In addition, I wondered about the care for residents without family or friends to advocate on their behalf. These experiences were the initial catalyst for pursuing my research questions in this dissertation about nursing home care.

If my family's experiences with nursing home care have sparked the energy behind the research, then my professional experiences have framed the direction. As an attorney at the U.S. Food and Drug Administration for many years, I often reflected how the pharmaceutical policies implemented by FDA, for which I provided legal counsel, were affecting individual patients. In particular, I wanted to know how, and to what extent, FDA regulatory steps and risk communications helped ensure safer use of medicines. These questions are also critical for the use of prescription analgesics in nursing homes. The outstanding training in epidemiology and public health that I have

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## **Abbreviations**

AAPM: American Academy of Pain Medicine

ADL: Activity of Daily Living

AGS: American Geriatric Society

AMDA: American Medical Directors Association

APS: American Pain Society

ASIPP: American Society of International Pain Physicians

CMS: Center for Medicare and Medicaid Services

CNS: Central Nervous System

CPS: Cognitive Performance Scale

ER: Extended-Release

FDA: Food and Drug Administration

IHCP: Information for Health Care Professionals

IOM: Institute of Medicine

MDS: Minimum Data Set

NSAID: Nonsteroidal Anti-Inflammatory Drug

OBRA: Omnibus Budget Reconciliation Act of 1987

OSCAR: Online Survey, Certification and Reporting

OTC: Over-the-Counter

PHA: Public Health Advisory

REMS: Risk Evaluation and Mitigation Strategy

SES: Socioeconomic Standing

WHO: World Health Organization



## **CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW**

## **Nursing home residents and their care**

Nursing home care is critical for the health of millions in the United States. In 2009 over 2.8 million Americans 65 years and older resided in a nursing home at some point during the year.<sup>1</sup> Over 1 million of these residents were 85 years and older. More elderly will reside in nursing homes as the American population grows. Nursing homes provide multiple services for residents, including housing, nutrition, and social services, as well as medical care and assistance with daily tasks. In 2012 there were nearly 16,000 nursing homes in the United States that were certified for Medicare and Medicaid reimbursement.<sup>2</sup>

Most elderly nursing home residents experience significant diseases and debilitating conditions related to older age. Four out of five nursing home residents need assistance with at least one basic “activity of daily living” (ADL) and three out of five need assistance with at least four ADLs.<sup>2</sup> Three out of five nursing home residents also have a moderate or severe cognitive deficit.<sup>2</sup> These figures demonstrate this population’s vulnerability.

A groundbreaking report in 2001 from the Institute of Medicine (IOM) brought to light numerous problems in the care for nursing home residents.<sup>3</sup> The IOM report identified critical care deficiencies in nursing homes, such as the high prevalence of pressure sores, malnutrition, and pain in residents, as well as the improper treatment of residents, including the use of physical and chemical restraints.<sup>3</sup> The IOM report acknowledged the limitations of nursing home resident and staff resources, as well as the important role of Medicare and Medicaid payment structures, for aspects of care. Despite these limitations, the report emphasized nursing homes should take immediate steps to

rectify these care problems, particularly resulting from neglect. The report then provided recommendations for improving resident access to needed services, strengthening external oversight of nursing homes, developing the work force, increasing organizational capacity, and addressing reimbursement issues.

### **Persistent non-cancer pain in nursing home residents**

The IOM identified the management of resident pain as a public health priority in nursing homes.<sup>3</sup> Before the 2001 IOM report was issued, studies estimated that between 45 to 80 percent of residents lived with some degree of pain that impaired their functioning and quality of life.<sup>4-6</sup> This common pain experience is caused by the higher prevalence of age-related conditions in the elderly, such as arthritis, musculoskeletal disorders and peripheral vascular diseases.<sup>7,8</sup> Pain in older individuals can cause functional impairment, falls, slow rehabilitation, and greater health-care use and costs.<sup>8-10</sup> In particular, pain in nursing home residents can diminish their physical and cognitive functioning and decrease their quality of life.<sup>5,11-13</sup> Many nursing home residents are particularly vulnerable to pain's ill effects because of their greater frailty and diminished resilience.<sup>7</sup>

In the last decade, studies have continued to find that a large proportion of residents experience significant pain.<sup>7</sup> The Institute of Medicine examined in 2011 the problem of pain in America and emphasized the vulnerability of nursing home residents to substantial pain and its debilitating effects.<sup>14</sup> Many studies have assessed pain in large nursing home sample populations using federal survey data.<sup>15-18</sup> In these studies the prevalence of pain, measured over a prior one-week period, have ranged from 4% for

daily pain that was excruciating at times;<sup>15</sup> 17% for daily pain that was moderate or severe;<sup>16</sup> and 22-23% for any pain.<sup>17,18</sup> Another study using federal survey data found that annual prevalence of moderate-to-severe pain, occurring within the past week, in residents decreased from 29% in 2006 to 22% in 2009.<sup>19</sup> Studies in smaller U.S. nursing home sample populations that relied on resident interviews and medical record reviews have identified greater percentages of residents in pain: 42% for more severe pain<sup>20</sup> and 51% for any pain.<sup>13</sup>

Persistent pain is longer in duration, typically defined as any pain occurring for at least a three-month period.<sup>21</sup> Cancer is one cause of persistent pain, but many nursing residents without cancer also experience lasting pain from diseases and health conditions.<sup>8</sup> One study estimated that nearly half of all nursing home residents experience some degree of persistent non-cancer pain (i.e., any degree of pain over a three-month period).<sup>21</sup> Studies have estimated that between 5-49 percent of nursing home residents experience persistent, non-cancer pain, depending on the duration and intensity threshold.<sup>12,21,22</sup> This persistent pain can range in intensity from mild to severe and is associated with more adverse health outcomes in residents.<sup>21</sup>

### **Treatment options for pain in nursing homes**

Analgesics are an important part of the nursing home's armamentarium for treating resident pain, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and prescription opioids. Studies have found that acetaminophen and NSAIDs can be effective for certain types of persistent pain in the elderly, such as low back pain and osteoarthritis.<sup>5,8,23</sup> However, there are safety concerns with these drugs in

the elderly, including hepatic toxicity from long-term acetaminophen use at high doses and serious and life-threatening gastrointestinal and cardiovascular adverse events from NSAIDs, including newer COX-2 inhibitors (like Celebrex®).<sup>5,8,23</sup>

Under this framework for balancing risk and benefits, opioids are another important treatment option for persistent non-cancer pain in the elderly. Prescription opioids have been used for decades to treat short, acute pain, as well as cancer pain.<sup>2</sup> Some studies suggest that prescription opioids can be appropriate for certain types of non-cancer persistent pain under a cautious approach that includes careful selection, titration, and monitoring.<sup>8,23,24</sup> Many of these drugs can be administered in different dosage forms, such as through oral, sublingual, and intravenous routes. There are two classes of opioids for temporal effects, either as immediate release for up to 4 hours duration or extended release for up to 24 hours duration.<sup>25,26</sup>

Despite this range of analgesic options, studies in nursing home populations have found that between 25 to 40 percent of nursing home residents with non-cancer pain do not receive any analgesics.<sup>7,21,27,28</sup> Due to this glaring gap, the IOM has encouraged greater use of analgesics, including opioids, for nursing home residents suffering from pain.<sup>14</sup> The IOM also stressed the need to update these findings on analgesic use, especially studies assessing the safety and effectiveness of opioids for persistent pain.

### **Appropriate selection and use of prescription opioids in nursing home residents**

In order for prescription opioids to successfully alleviate persistent non-cancer pain for nursing home residents, the drugs must be used carefully under the proper conditions. The reliance on pharmaceutical therapies can be effective for many

conditions and types of pain if nursing home practitioners carefully select, administer and monitor the prescription drug use.<sup>8,24,29</sup> However, inappropriate drug prescribing can threaten patient safety because of adverse effects. The elderly are particularly vulnerable because of their pharmacokinetic and pharmacodynamic differences from the general population and diminished resilience.<sup>8,24,29</sup> In addition, the co-prescribing of drugs can harm patients from interactive effects.<sup>30</sup> Because nursing home residents take numerous pharmaceuticals (at least 8 on average), the risks for drug interaction are much higher.<sup>31</sup> The administration of numerous drugs to an individual (“polypharmacy”) has been identified as a serious risk factor for adverse events in nursing homes.<sup>31,32</sup>

These risks can be heightened in the nursing home setting, where inappropriate prescribing is an important concern. One study estimated that over 50 percent of elderly nursing home residents receive at least one potentially inappropriate prescription each year.<sup>33</sup> Nursing home residents are particularly vulnerable to the harms from inappropriate opioid prescribing because they use more medications and have more comorbid conditions.<sup>32,34,35</sup> One study in the elderly found that 26% of patients with osteoarthritis were inappropriately prescribed an opioid because of potentially dangerous interactions with other drugs taken by the patients.<sup>30</sup> The co-prescribing of other CNS drugs, such as atypical antipsychotics and antidepressants, with opioids increases the risks for psychoactive adverse events, including delusions and sedation.<sup>36</sup> These findings demonstrate how opioid prescribing decisions must account for multiple patient factors, including co-prescribing for other conditions.

## **Practice guidelines for persistent non-cancer pain care and pharmaceutical use**

Public health and health care organizations have attempted to respond to this acute need for improved pain management in the United States, including in nursing homes. These organizations play an important role in the treatment of persistent non-cancer pain, including the use of prescription drug therapies, through policy and practice recommendations. These recommendations attempt to help practitioners make more informed decisions about analgesic prescribing for patients. Simply increasing the frequency of analgesic prescribing in the nursing home population will not, by itself, ensure better pain management. Instead, the goal is to ensure that more patients, such as nursing home residents, have their pain managed safely and effectively.

The World Health Organization (WHO) provided the foundation for these pain management recommendations in addressing pharmaceutical therapies for cancer pain. The WHO established a three-step “ladder” approach for persistent pain management in cancer patients that has also been applied to non-cancer patients.<sup>37</sup> Under this approach, non-opioids should be administered first for the patient’s pain. If these are insufficient, then opioids for mild-to-moderate pain (such as codeine) can be administered next in conjunction with the non-opioid. Finally, opioids for moderate-to-severe pain (such as morphine) can be administered as a final step in conjunction with the non-opioid. For each of these steps, an adjuvant drug may also be administered.

Many organizations have recommended practices for pain management and analgesic use based on their own review of the evidence,<sup>38</sup> including the American Pain Society (APS) and American Academy of Pain Medicine (AAPM),<sup>39</sup> as well as the American Society of International Pain Physicians (ASIPP).<sup>40</sup> The American Geriatric

Society (AGS) recently issued practice guidelines for the use of analgesics, including opioids, in elderly adults with persistent pain.<sup>8</sup> The AGS reviewed three categories of analgesics – acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids. Following the WHO guidelines for cancer pain use, the AGS recommended that these analgesics be carefully selected for the individual patient, initiated at low doses and slowly titrated upwards if necessary, and include regular monitoring and frequent dosage reassessment.<sup>8</sup> The AGS emphasized potential adverse effects from opioids, such as from the failure to follow labeling instructions for contraindications and proper dosing.<sup>8</sup>

The American Medical Directors Association (AMDA) has published a practice guideline for pain management in nursing homes and addressed the role of prescription drugs, including opioids.<sup>24</sup> The AMDA guidelines emphasize that nursing homes should follow the stepped approach in the WHO guidelines for analgesic use.<sup>24</sup> The guidelines also recommend that nursing homes carefully titrate the analgesic dose and monitor the drug's safety and effectiveness in each resident over time.<sup>24</sup> For monitoring, the guideline stresses the need for an ongoing assessment of each nursing home resident's ability to perform ADLs and their cognition.<sup>24</sup>

### **Role of federal agencies for nursing home and pharmaceutical oversight**

Two federal agencies also play an important role in these efforts to improve nursing home care for residents and their analgesic use: the U.S. Centers for Medicare and Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA). CMS has regulatory authority over nursing home, while FDA has regulatory authority over prescription drugs. After passage of the Omnibus Budget Reconciliation Act of 1987



(OBRA), which provided greater federal authority over nursing homes receiving Medicaid and Medicare reimbursements, CMS issued nursing home regulations in the 1990's to ensure better care for residents, as well as guidelines for pain management (F309) and prescription drug use (F329).<sup>3,41</sup>

The CMS pain management guideline emphasizes that prescription opioid drugs should be selected and dosed in accordance with current standards of practice.<sup>41</sup> The guideline states that careful titration and monitoring for the drug's safety and effectiveness is necessary.<sup>41</sup> The prescription drug guideline warns against a drug's use in excessive dose or duration and with inadequate monitoring for effectiveness and safety.<sup>41</sup> CMS works with states to inspect nursing home facilities to assess compliance with these guidelines.<sup>41</sup>

FDA also plays an important role in ensuring appropriate pharmaceutical use by regulating the approval, manufacturing, and marketing of prescription drugs, including analgesics. FDA must evaluate each prescription drug's safety and efficacy before the agency can approve that drug for a specific use. FDA also must approve the drug's labeling, specifying the indications for which the drug is effective, as well as the safe conditions for use.<sup>42</sup> The labeling includes any warnings and cautions about possible side effects, including safety risks to specific types of patients and potential dangerous interactions with other drugs.<sup>42</sup>

Importantly, FDA generally does not regulate prescribing decisions by medical practitioners, including within nursing homes. Because FDA does not regulate the practice of medicine, health care practitioners can use an approved drug for an individual patient in a different way from the indications and conditions in the drug labeling.<sup>43</sup> This

“off-label use” should be based on the practitioner’s professional judgment, which can be based on more recent medical and scientific knowledge, such as described in practice guidelines.<sup>43</sup> Despite this discretion given to medical professionals by FDA, nursing home practitioners must carefully consider FDA’s critical judgment how the drug may be safely used, as reflected in the approved labeling conditions. Although FDA does not regulate analgesic prescribing decisions for nursing home residents, CMS guidelines recommend that nursing homes follow FDA labeling conditions for drug prescribing.<sup>41</sup>

FDA has other regulatory tools after a drug’s approval to help ensure safe use. FDA can strengthen warnings on the drug’s labeling (e.g., a “Black Box” warning) to identify more clearly for health care practitioners the most important risks.<sup>44</sup> FDA can also inform patients and health care providers about potential risks from adverse events through safety communications on its website and outreach to stakeholder groups.<sup>44,45</sup> In addition, FDA can implement a Risk Evaluation and Mitigation Strategy (REMS) that includes special conditions for prescription drug use. Questions have been raised, though, if these additional steps have minimized the targeted drug risks.<sup>44,46</sup>

### **FDA steps for prescription opioids**

FDA’s role in ensuring prescription drug safety has been particularly visible in the agency’s regulation of opioids. Deaths and serious injury resulting from opioid overdose have been a significant public health concern in recent years.<sup>47</sup> Despite recent attention on prescription opioid misuse in the general population, addiction is not a significant concern for elderly nursing home residents.<sup>4</sup> However, a significant portion of adverse events have occurred in patients taking the opioid drug as prescribed.<sup>39,40</sup>

Extended-release (ER) prescription opioids in particular have faced heightened scrutiny about safety risks.<sup>45</sup> FDA approved ER formulations for opioids that provide a longer drug release in the patient's body.<sup>26</sup> Oxycodone hydrochloride ("oxycodone") ER and transdermal fentanyl ("fentanyl") ER, available since the 1990's, are widely used opioids in nursing homes.<sup>21,48</sup> Although effective in treating more serious pain over a longer duration, these drugs can increase a patient's risk for adverse effects, such as overdose and severe respiratory depression, particularly upon first being administered and for the elderly.<sup>49-52</sup> The FDA-approved labeling warns of this risk and emphasizes that these drugs are only for use in patients with moderate-to-severe, continuous pain.<sup>49,50</sup>

Each prescription opioid has additional cautions and warnings, depending on the safety evidence for that drug. For example, the fentanyl ER labeling warns that opioid-naïve patients (who have not first tried another short-acting opioid drug) should not be prescribed the drug because of the risks for respiratory depression and overdose. The oxycodone ER labeling cautions against use of the drug in combination with other central nervous system (CNS) depressants, which creates serious risks in patients for fatal respiratory depression, profound sedation, or coma.<sup>50,51</sup> The labeling in both drugs also warns that the elderly are even more susceptible to these side effects.<sup>50,53</sup>

Health care practitioners must carefully select an opioid for an individual's persistent pain based on these different safety concerns and warnings. However, it is not clear if these warnings have ensured safer use, particularly in nursing homes. In fact, one study found that ER opioids were commonly prescribed in opioid-naïve nursing home residents in Rhode Island during 2004-2005 despite the FDA labeling statements. Since

this time, FDA has taken additional regulatory steps beyond the labeling to ensure safer ER opioid use.

First, FDA issued multiple communications in successive years to physicians and the public about transdermal fentanyl risks, including that opioid-naïve patients should not be initiated on the drug.<sup>54</sup> Second, FDA implemented a Risk Evaluation and Mitigation Strategy (REMS) in 2012 for ER opioids such as transdermal fentanyl and oxycodone that provides additional precautionary steps for their prescribing, such as healthcare provider training about the risks and appropriate use.<sup>55</sup> FDA, though, did not target these steps at the use of prescription opioids in nursing home residents, and it is not clear if they are reducing inappropriate prescribing in nursing homes.

### **Disparities within nursing homes**

Much attention has been focused in recent years on disparities in health care in the United States. Studies have found that certain subpopulations, particularly with lower socioeconomic standing (SES) and minority groups, suffer disproportionately worse health outcomes than others, such as chronic diseases and life expectancy.<sup>56</sup> These divisions exist between and within nursing homes themselves, depending on the facility and resident characteristics.<sup>3</sup> These disparities are even more troubling considering that nursing home residents are a more vulnerable population compared to otherwise similar individuals (i.e., community-living seniors) in the U.S. population.<sup>3</sup>

The outcomes affected by nursing home disparities include the adequacy of care for residents, such as pain management and appropriate analgesic prescribing. The IOM expressed significant concerns in its 2001 and 2010 reports that pain treatment lags

further behind for certain individuals and at specific facilities.<sup>3,14</sup> Prior studies have identified disparities in pain management for nursing home residents who are non-white<sup>57</sup> or cognitively impaired.<sup>58</sup> Other studies have found that non-white, older, and cognitively impaired residents are less likely to receive analgesics for non-cancer pain<sup>12,27</sup> and cancer pain.<sup>59</sup> In addition, certain facility characteristics, such as for-profit status, have been associated with worse health outcomes for residents.<sup>60</sup> Thus, efforts to improve prescribing practices for resident pain must also focus on even more vulnerable subpopulations within nursing homes, rather than simply using a general approach across all types of nursing homes and residents.

### **Conceptual framework**

The analytic framework for this research, assessing nursing home analgesic prescribing for persistent pain, can be organized in the following steps:

1. Nursing homes must first identify a resident's persistent pain.
2. Once identified, nursing homes can provide an analgesic as part of a therapeutic approach. These analgesic options are acetaminophen, NSAIDs, and short-acting (i.e., immediate release) opioids, depending on the frequency, duration, and type of pain. Practice guidelines, CMS requirements, and FDA regulatory steps (such as drug labeling) are critical external factors that inform and shape this decision.
3. If these different options for analgesic therapy do not adequately treat the resident's persistent pain, then nursing homes can consider a prescription long-acting (i.e., extended release) opioid as a possible option. Transdermal fentanyl ER is the example in our model. Practice guidelines and federal regulation also

inform and shape this prescribing decision. FDA-approved drug labeling and communications emphasize that the drug should only be initiated in patients who

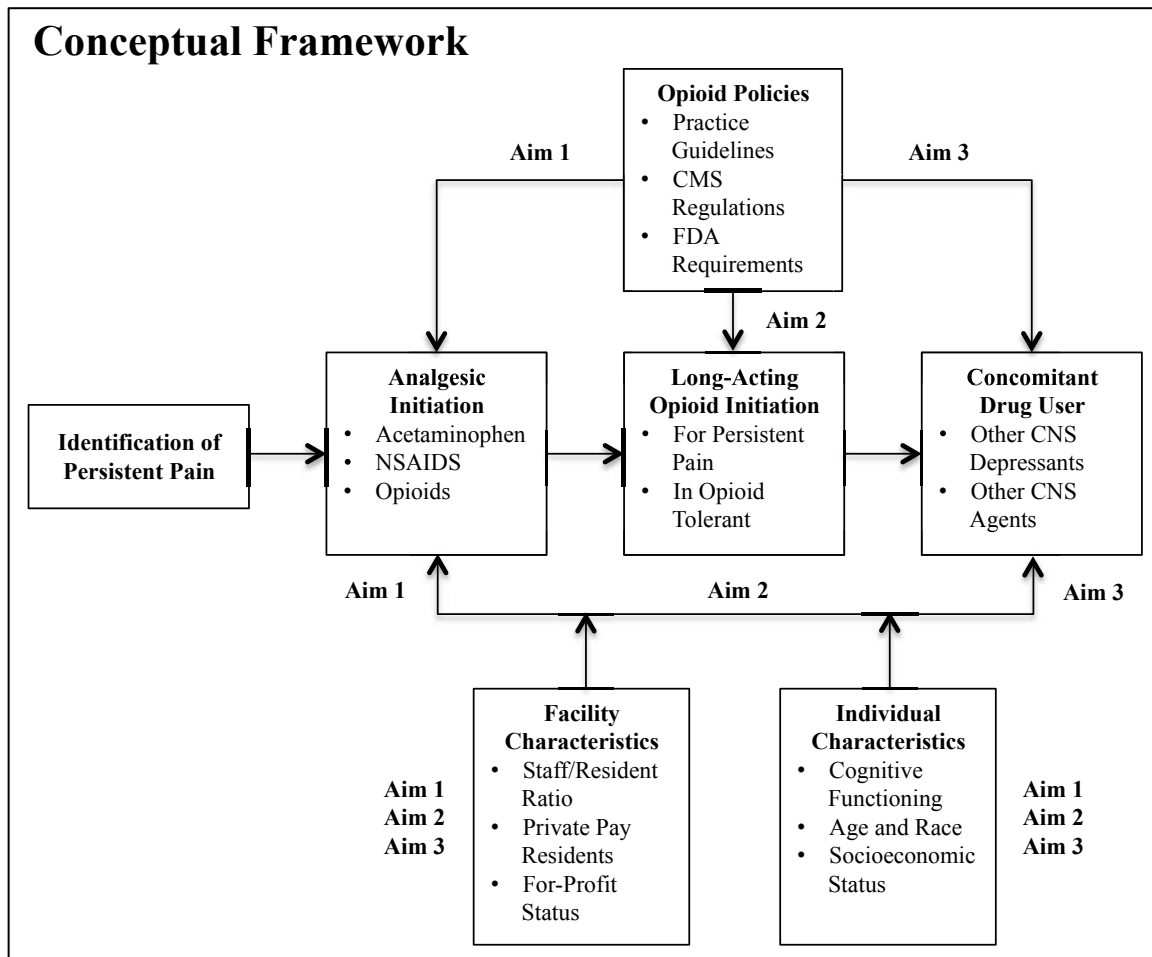
- have moderate-to-severe, persistent pain and
- are opioid tolerant (i.e., have already taken an opioid and are thus not opioid naïve)

4. For these long-acting opioid prescribing decisions, nursing homes must also consider the other drugs that residents take for possible interaction effects. Again, practice guidelines and federal regulation can shape these decisions. Oxycodone ER is the example in our model. Considerations for drug interactions are relevant as the opioid therapy is

- initiated (i.e., accounting for other currently prescribed drugs) and then
- maintained in the future (accounting for future decisions about other drugs)

5. Along this treatment continuum, disparities in pain management and appropriate prescribing can influence nursing home decisions about residents' therapies in steps 2, 3, and 4.

**Figure 1.1. Conceptual Framework for Analgesic Prescribing in Nursing Homes.**



## **Dissertation goals and specific aims**

### Overall Goal of the Dissertation

The dissertation's overall goal is to assess the appropriateness of analgesic prescribing in elderly nursing home residents. The dissertation examines the prescribing of any analgesics for residents with persistent pain, as well as the prescribing of certain ER opioids for residents regardless of pain experience.

The main goals are to:

- Assess the prevalence of analgesic prescribing (e.g., acetaminophen, NSAID, and opioid drugs) for elderly residents with persistent pain and identify any associations between no prescribing and individual and facility characteristics;
- Assess the prevalence of transdermal fentanyl ER prescribing in elderly residents who are opioid-naïve (i.e., non-compliant with FDA labeling) and identify any associations between no prescribing and individual and facility characteristics; and
- Assess the prevalence of concomitant prescribing of CNS depressants and other CNS agents with oxycodone ER (i.e., non-compliant with FDA labeling) in elderly residents and identify any associations between concomitant prescribing and individual and facility characteristics.

Specific Aim 1: To assess prescription analgesic utilization and the characteristics of prescription analgesic use for persistent non-cancer pain in elderly nursing home residents in the United States.

*Hypothesis 1: We hypothesize that resident characteristics (poorer cognitive functioning, older age, lower socioeconomic status, and non-white race) and facility characteristics (smaller staff-to-resident ratio, fewer private pay residents, and for-profit status) will be associated with lower incident use of analgesics, including opioids, for persistent non-cancer pain.*

Specific Aim 2: To assess the prevalence of non-adherence in nursing home residents to conditions established by the U.S. Food and Drug Administration for transdermal



fentanyl initiation, and to identify patient and facility characteristics associated with non-adherence.

*Hypothesis 2: We hypothesize that adherence to these conditions for transdermal fentanyl initiation will be lower for residents who have poorer cognitive functioning, older age, lower socioeconomic status, or are not white and in nursing home facilities that have smaller staff-to-resident ratio, fewer private pay residents, and are for-profit.*

Specific Aim 3: To assess the prevalence in nursing home residents of central nervous system (CNS) drug co-prescribing with extended-release oxycodone and adherence to conditions established by the U.S. Food and Drug Administration for extended-release oxycodone use, and to identify patient and facility characteristics associated with non-adherence.

*Hypothesis 3: We hypothesize that adherence to these conditions for extended-release oxycodone use will be lower for residents who have poorer cognitive functioning, older age, lower socioeconomic status, or are not white and in nursing home facilities that have smaller staff-to-resident ratio, fewer private pay residents, and are for-profit.*

### Organization of this Dissertation

Chapter 1 (this chapter) provides the pertinent background for the research and reviews the relevant literature. Chapter 2 assesses the prevalence of analgesic prescribing for elderly nursing home residents with persistent non-cancer pain and analyzes whether certain individual or facility characteristics are associated with no analgesic prescribing for this pain. Chapter 3 assesses the prevalence of transdermal fentanyl ER prescribing in

elderly nursing home residents who are opioid-naïve and analyzes whether the individual or facility characteristics (from the prior model) are associated with opioid-naïve prescribing, in contrast to FDA warnings. Chapter 4 assesses the prevalence of concomitant prescribing of CNS depressants and other CNS agents with oxycodone ER and analyzes whether the individual or facility characteristics (from the prior models) are associated with opioid-naïve prescribing, in contrast to FDA warnings. Each chapter is a separate, unique manuscript and includes individual appendices. Chapter 5 presents a summary of the findings and the conclusion.

#### Data Sources

This dissertation relied on data for all U.S. nursing home residents during 2007-2008 from the Minimum Data Set (MDS); the Online Survey, Certification and Reporting (OSCAR) database; and Medicare Part D.

The MDS is a standardized survey instrument measuring each nursing home resident on fifteen domains, including any degree of pain, cognitive and physical functioning, psychosocial well-being, activities and diseases.<sup>61</sup> The MDS assessor, a trained nursing home staff person, relies on personal observation, interviews with residents, resident medical records, discussions with resident family, and consultation with clinicians and other staff to complete the MDS questions and record all information on the MDS forms.<sup>61,62</sup> The information gathered for the MDS is then used by the nursing home to develop individual care plans for each resident.<sup>3,62</sup> The nursing home assesses each resident every three months for certain MDS measures (including cognitive and physical functioning, mood, and pain) and annually for all MDS measures and when any

significant change in resident status occurs.<sup>61</sup> A revised version of the MDS (MDS 2.0) was used during our 2007-08 study period. The MDS 2.0 measures in this dissertation have been found generally reliable and valid for the domains when used by trained staff.<sup>63</sup> For example, MDS 2.0 items have been incorporated into other valid and reliable instruments (e.g., MDS ADL Scale, MDS Cognitive Performance Scale) to measure resident characteristics, such as physical and cognitive functioning.<sup>63-65</sup>

The dissertation also relied on OSCAR data for measurement of facility factors, such as the facility's staff-to-resident ratio, percentage of private pay residents, for-profit status, and compliance with federal law. The federal government compiles annually in OSCAR this information about each nursing home facility.<sup>66</sup> Finally, the dissertation relied on Medicare Part D claims to determine analgesic and other prescribing for residents in our population. This data includes the drug, dose, dosage form, and length of prescription (e.g., 30 days).<sup>67</sup>

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**CHAPTER 2: FREQUENCY AND PREDICTORS OF  
ANALGESIC PRESCRIBING IN U.S. NURSING HOME  
RESIDENTS WITH PERSISTENT PAIN**

## **Abstract**

Objective: To quantify prescription analgesic use among elderly nursing home residents with persistent non-cancer pain and to identify individual and facility traits associated with the absence of such treatment.

Design: Cross-sectional study.

Setting: Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims.

Participants: From a cross-section of all long-stay U.S. nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified individuals  $\geq 65$  years old with persistent non-cancer pain, but without Alzheimer's, severe cognitive impairment or receipt of hospice care.

Measurements: Residents with moderate-to-severe, daily pain on consecutive assessments at least 90 days apart comprised our cohort with persistent pain. We identified Part D dispensing for an opioid or non-steroidal anti-inflammatory (NSAID) within 30 days of persistent pain onset. Resident and facility characteristics were obtained from MDS and OSCAR records. We estimated associations of patient and facility attributes and pain treatment from multilevel mixed effects logistic regression analyses.

Results: Among 18,526 residents with persistent pain, 3,094 (16.7%) did not receive prescription pain medicine; 12,815 (69.2%) received a prescription opioid; 485 (2.6%) received a prescription NSAID; and 2,132 (11.5%) received a prescription opioid and NSAID. In the regression analysis with adjustments, residents who were older (compared to ages 65-74, ages 75-84 odds ratio (OR)=1.30 , 95% CI=1.16-1.47; ages 85-94 OR=1.63 , 95% CI=1.44-1.85; ages  $\geq$ 95 OR= 2.06, 95% CI=1.70-2.49); Black (compared to White residents, OR=1.20, 95% CI= 1.03-1.39); and more cognitively impaired (compared to no cognitive impairment, borderline intact OR=1.11, 95% CI=0.97-1.27; mild impairment OR=1.31 , 95% CI=1.15-1.49; moderate impairment OR=1.62, 95% CI=1.42-1.83; moderate-to-severe cognitive impairment, OR=2.12, 95% CI = 1.71-2.62) were less likely to receive a prescription pain medicine.

Conclusion: Pain remains incompletely treated in U.S. nursing homes, especially among certain subpopulations of residents such as those with cognitive impairment. Changes in pain management practice and policies may be necessary to target these more vulnerable residents.

## INTRODUCTION

Nursing home care is critical for the health of millions in the United States. Nearly 3 million Americans aged 65 years and older resided in a nursing home at some point in 2009, and over 1 million of these residents were 85 years and older.<sup>1</sup> More elderly will reside in nursing homes as the American population grows. In 2009 there were nearly 16,000 nursing homes in the United States that were certified for Medicare and/or Medicaid reimbursement.<sup>1</sup>

Most elderly nursing home residents experience significant diseases and debilitating conditions related to older age, including persistent pain. Such pain usually occurs for at least three months and can vary in intensity.<sup>2</sup> Prior studies have found that between 45 to 80 percent of residents experience some degree of pain that impairs functioning and quality of life,<sup>3</sup> and that 5 to 49 percent of residents have persistent non-cancer pain, depending on the duration and intensity threshold.<sup>2,4,5</sup> This common pain experience is caused by the higher prevalence of age-related conditions in the elderly, such as arthritis, musculoskeletal disorders, and peripheral vascular diseases.<sup>6</sup> Pain in older individuals can adversely affect their physical functioning, mental health, and social engagement, as well as create greater health-care use and costs.<sup>7-9</sup> These damaging effects have also been found in elderly nursing home residents and can severely limit their quality of life.<sup>6,10,11</sup> Many nursing home residents are particularly vulnerable to pain's ill effects because of their greater frailty and diminished resilience.<sup>6</sup>

A recent report by the Institute of Medicine (IOM) stressed the importance of improved pain management in nursing homes.<sup>12</sup> Analgesics are an important part of the nursing home's armamentarium for treating resident pain, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and prescription opioids. However,

studies have found that between 25 to 40 percent of nursing home residents with non-cancer pain did not receive any analgesics.<sup>2,6,11</sup> Due to this glaring gap, the IOM and professional societies have encouraged greater use of prescription analgesics for nursing home residents suffering from persistent pain.<sup>7,12</sup> The IOM emphasized the need to update these study findings on analgesic use.<sup>12</sup>

Even if analgesic prescribing has increased in this population with persistent pain over recent years, there remains concern that treatment may lag behind for more vulnerable subpopulations within nursing homes and at specific types of facilities. Prior studies have identified disparities in pain management for nursing home residents who are non-white<sup>13</sup> or cognitive impaired.<sup>14</sup> Other studies have found that non-white, older, and cognitively impaired residents are less likely to receive analgesics for non-cancer pain<sup>5,11</sup> and cancer pain.<sup>15</sup> In addition, certain facility characteristics, such as for-profit status, have been associated with worse health outcomes for residents.<sup>16</sup>

In response to the IOM's call for updated research on these questions, we assessed data on nursing home residents, facilities, and medication prescribing in 2007-2008 from the national Minimum Data Set (MDS), the Online Survey, Certification, and Reporting (OSCAR) database, and Medicare Part D to evaluate the extent of analgesic prescribing for elderly nursing home residents with persistent non-cancer pain, defined as moderate-to-severe pain lasting at least 3 months. We also assessed if certain individual and facility-level factors were associated with no analgesic use for these residents with persistent non-cancer pain.

## METHODS

### *Participants*

Our source population was the approximately 2.99 million individuals aged 65 and older who resided in nursing homes in the United States at any time between December 1, 2007, through November 30, 2008, and had an MDS record.

*Inclusion Criteria.* We limited our analysis to the 53% of elderly residents with at least two MDS assessments over a 90-day period or longer (Figure 2.1). We then included in our study those individuals from the source population who had persistent non-cancer pain, defined as moderate-to-severe pain lasting 3 months or longer.<sup>2</sup> Each nursing home resident is assessed in the MDS at least every 3 months for the frequency and intensity of any pain over the previous 7 days.<sup>17</sup> This measurement has been found valid for measuring pain frequency and intensity in a scored scale.<sup>18</sup> For our study, a nursing home resident was considered in persistent pain if the individual had two consecutive MDS reports, at least 90 days apart but no more than 180 days apart, with moderate or severe pain daily during the prior 7-day period. We used this pain intensity definition (moderate-to-severe) to match the guideline recommendations for analgesic use. We defined “persistent pain onset” as the date of the second MDS pain assessment satisfying the persistent pain definition, yielding a population of 59,114 individuals (3.8% of eligible source population).

*Exclusion Criteria.* We excluded those individuals who had cancer, were terminally ill, or had Alzheimer’s disease or most severe cognitive impairment, defined as an MDS Cognitive Performance Scale (CPS) score of 5 or 6 (Figure 2.1). We excluded the most cognitively impaired because of the difficulty in assessing accurately

their pain levels.<sup>14</sup> We also excluded those individuals who had not resided in the nursing home for at least 90 continuous days at persistent pain onset. After these exclusions, 22,943 individuals remained in our study population. We then excluded 2,776 residents (12.1%) who did not have any Part D prescription drug records during the time period. Next, we excluded 1,018 individuals (5.0%) who resided in hospital-based facilities. Finally, data were missing for at least one covariate for 623 of the 19,149 participants (3.3% of the sample). We dropped these subjects from the analysis. Our study population then consisted of 18,526 individuals (Figure 2.1).

### *Measures*

We analyzed data about each nursing home resident from the MDS, a standardized survey instrument that measures each resident on fifteen domains, including pain status, cognitive and physical functioning, psychosocial well-being, activities and diseases.<sup>17</sup> All U.S. nursing homes (certified for Medicare and/or Medicaid) are required by federal law to use the MDS survey instrument to assess periodically each nursing home resident.<sup>19</sup> The MDS assessor, a trained nursing home staff person, relies on personal observation, interviews with residents, resident medical records, discussions with resident family, and consultation with clinicians and other staff to complete the MDS questions and record all information on the MDS forms.<sup>17,20</sup> The information gathered for the MDS is then used by the nursing home to develop individual care plans for each resident.<sup>19,20</sup> The nursing home assesses each resident every three months for many MDS measures (e.g., cognitive and physical functioning, mood, and pain) and annually for all MDS measures and when any significant change in resident status occurs.<sup>17</sup>



Our study relied on the MDS 2.0 version, which was used during our 2007-08 study period. The MDS 2.0 measures in our study have been found generally reliable and valid for the domains when used by trained staff.<sup>21</sup> For example, MDS 2.0 items have been incorporated into valid and reliable instruments (e.g., MDS ADL Scale, MDS Cognitive Performance Scale) to measure resident characteristics, such as physical and cognitive functioning.<sup>21-23</sup>

We also relied on OSCAR data for measurement of facility factors, such as the facility's staff-to-resident ratio, percentage of private pay residents, for-profit status, and compliance with federal law. The federal government compiles annually in OSCAR this information about each nursing home facility.<sup>24</sup> Finally, we analyzed each resident's drug prescribing using Medicare Part D records. This data includes the drug, dose, dosage form, and duration (e.g., 30 days).<sup>25</sup>

*Analgesic Prescribing.* Our primary outcome was whether each resident with persistent non-cancer pain failed to receive a prescription for an opioid or non-steroidal anti-inflammatory drug (NSAID). Our definition of an opioid prescription included mu agonist opioids (codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, and propoxyphene) and dual mechanism opioids (tramadol), as well as prescription drugs with these opioid active ingredients in combination with other analgesic ingredients, such as hydrocodone or oxycodone with acetaminophen (Figure 2.2). Our definition of NSAIDs included newer Cox-II inhibitors, such as Celebrex (Figure 2.2). We did not include over-the-counter (OTC) acetaminophen or NSAIDs in the analgesic definition, because Part D does not cover OTC drugs<sup>25</sup> and our study focuses on the most substantial (moderate-to-severe)

persistent pain. We characterized those residents with an analgesic prescription dated within 30 days before or after persistent pain onset under our definition as having an analgesic prescription. We also assessed other alternative pain treatments recorded in the Part D or MDS records within this 30-day window, such as different prescription drugs (i.e., muscle relaxants, steroids, and gabapentin) and physical therapy.

*Covariates.* We evaluated whether certain individual and facility factors were associated with not having an analgesic prescription. For individual factors, we hypothesized that older age, poorer cognitive functioning, lower socioeconomic status (SES), and non-white race/ethnicity would be associated with less analgesic prescribing. We measured cognitive functioning in the MDS measurement (at persistent pain onset) based on the CPS score from 0 (intact) to 4 (moderate-to-severe impairment). We measured SES based on highest completed education level and whether the resident paid for nursing home non-medical services out-of-pocket (“self-pay”). For facility factors, we hypothesized that smaller staff-to-resident ratio, fewer private pay residents, and for-profit status would be associated with less analgesic prescribing. We obtained these facility measurements from the most recent OSCAR survey before persistent pain onset.

We also identified potential confounders that could be associated with these individual and facility factors and analgesic prescribing: gender, physical impairment, mood, family support, and facility compliance with federal law. We measured physical impairment in the most recent MDS (at or before persistent pain onset) by the degree of assistance needed for activities of daily living (ADLs) under the Morris Additive Scale from 0 (no help required) to 28 (most help needed); mood at the time of persistent pain onset by the MDS Mood Scale score from 0 (no mood symptoms) to 8 (most mood

symptoms); family support based on whether a family member or significant other participated in the most recent MDS care plan meeting (at or before persistent pain onset); and compliance with federal law based on whether there were any significant outstanding legal violations of federal nursing home requirements, as recorded in the most recent OSCAR survey before persistent pain onset.

### *Statistical Analysis*

We first assessed the proportion of residents in our study population with non-cancer pain who received a prescription analgesic. To test our hypothesis that certain individual and facility factors were associated with no analgesic prescribing for residents in persistent non-cancer pain, we fit a series of logistic regression models with no analgesic prescribing (versus analgesic prescribing) as the outcome.

The first models were univariate logistic regressions with one of the following predictors per model: age (categorized as <65 years,  $\geq 65$  to 74 years,  $\geq 75$  to 84 years,  $\geq 85$  years); race/ethnicity (White, Black, Hispanic, Asian, and other); cognitive functioning (categorized from 0-4 on the CPS Scale); self-pay status (yes versus no); education level (categorized as less than high school graduate, high school graduate, or college graduate/graduate school); facility staff hours per resident (categorized as <2.5 hours,  $\geq 2.5$  to 3.0 hours,  $\geq 3.0$  to 3.5-hours,  $\geq 3.5$  to 4 hours,  $\geq 4.0$  to 4.5 hours,  $\geq 4.5$  hours); facility proportion of self-pay residents (categorized as <10%,  $\geq 10\%$  to 30%,  $\geq 30\%$  to 50%,  $\geq 50\%$ ); and facility for-profit status (yes versus no). We also conducted the univariate logistic regression for each confounder in our model: gender; degree of ADL assistance (categorized as 0, 1-7, 8-14, 15-21, 22-28 from the Morris Additive

Scale), MDS Mood Scale (categorized as 0, 1-2, 3-4, 5-6, 7-8); family support (yes versus no); and facility compliance with federal law (yes versus no).

The next model included all of these variables in a multilevel logistic regression. Because residents are clustered within nursing homes and nursing homes are clustered within states, we included random effects (i.e., intercepts) in all models for these two levels to ensure more accurate standard errors. We also conducted sensitivity analyses using more stringent definitions of persistent pain (i.e., at least 3 consecutive MDS assessments with serious pain at least 90-180 days apart; at least 2 consecutive MDS assessments with serious pain at least 90-120 days apart). In addition, because different diseases and health conditions can cause persistent pain, we conducted subgroup analysis in those residents with arthritis, diabetes, back pain, and osteoporosis, as recorded in the MDS. Data were analyzed using SAS and Stata 13 software.

## **RESULTS**

### *Subject Characteristics*

Of the nearly 3 million elderly nursing home residents in our source population, nearly 60% had at least one MDS assessment with some degree of pain, including 22% with at least one episode of moderate or severe pain experienced on a daily basis for the prior 7 days (Figure 2.3). Only 3.8% of eligible residents had persistent pain under our definition (i.e., at least 2 consecutive MDS assessments at least 90, but no more than 180, days apart with moderate or severe pain on a daily basis).

Overall, 16.7% of participants with persistent non-cancer pain did not receive an analgesic prescription, while 53.0% received only an opioid/acetaminophen combination drug, 16.2% received only an opioid, 8.9% received both an opioid/acetaminophen

combination drug and a prescription NSAID, 2.7% received both an opioid and a prescription NSAID, and 2.5% received only a prescription NSAID (Table 2.1).

### *Differences in Characteristics by Prescribing Status*

Participants who did or did not receive a prescription analgesic differed by gender, age, race, cognitive impairment, self-pay status, facility hours per resident, facility proportion of self-pay residents, facility for-profit status, physical impairment, mood, and family support (all  $p \leq 0.001$ ) (Table 2.2). There was no significant difference by resident education level ( $p=0.152$ ) or facility compliance with federal law ( $p=0.817$ ) (Table 2.2). Of those residents not receiving any prescription analgesic, only a small percentage received other drugs prescribed for pain (muscle relaxant=3.9%, steroid=5.7%, gabapentin=10.5%) and only 8.6% received at least one day of physical therapy (Table 3). Participants who did not have a prescription analgesic also had lower percentages for receipt of other prescribed drugs compared to those who had a prescribed analgesic (Table 2.3).

### *Multivariate Associations*

Not receiving a prescription analgesic was associated with many individual resident factors (Table 2.4). In the multivariable logistic model, after accounting for mood, physical impairment, family support, and facility compliance with federal law, residents had a greater odds for no analgesic prescribing if they were male (compared to female, OR=1.38, 95% CI 1.24-1.53) older (compared to ages 65-74, ages 75-84 OR=1.30, 95% CI 1.16-1.47; ages 85-94 OR=1.63, 95% CI 1.44-1.85; ages  $\geq 95$  OR=2.06, 95% CI 1.70-2.49); more cognitively impaired (compared to intact cognitive functioning, borderline intact OR=1.11, 95% CI 0.97-1.27; mild impairment OR=1.31,

95% CI 1.15-1.49; moderate impairment OR=1.61, 95% CI 1.42-1.83; moderate-severe impairment OR=2.12, 95% CI 1.71-2.62); Asian (compared to White, OR=1.97, 95% CI 1.22-3.20) or Black (compared to White, OR=1.20, 95% CI 1.03-1.39); paid charges on their own (“self-pay” compared to non-self pay, OR=1.40, 95% CI 1.23-1.59); and had more education (compared to education less than high school graduate, high school graduate OR=1.10, 95% CI 1.01-1.21; college or graduate education OR=1.19, 95% CI 1.00-1.40).

The facility factors were not statistically significantly associated with no analgesic prescribing, except the facility’s proportion of self-pay residents in two categories had lower odds for no analgesic prescribing (compared to facilities with <10% self-pay residents,  $\geq 10\%$  to 30% OR=0.80, 95% CI 0.71-0.91;  $\geq 30\%$  to 50% OR=0.77, 95% CI 0.66-0.91) and the facility’s average staff hours per resident in three categories (compared to facilities with < 2.5 average staff hours per resident, 2.5-3.0 hours OR=0.80, 95% CI 0.67-0.98; 3.0-3.5 hours OR=0.83, 95% CI 0.69-0.99; 3.5-4.0 hours OR=0.80, 95% CI 0.66-0.97).

In the sensitivity analyses, as well as subgroup analysis for residents with arthritis, the individual factors of increasing age, greater cognitive impairment, and self-pay status were also statistically significantly associated with no analgesic prescribing (Appendices S2.A and S2.B). In the model with the shortest time window (90-120 days rather than 90-180 days), the association between no analgesic prescribing and increasing cognitive impairment was even stronger (compared to intact functioning, moderate-severe impairment OR=2.20, 95% CI=1.68-2.88). For diabetic residents, Asian race (compared to White, Asian OR=2.52, 95% CI=1.33-4.79) and cognitive impairment

(compared to intact functioning, moderate-severe impairment OR=2.36, 95% CI=1.63-3.40) were even more strongly associated with no analgesic prescribing.

## DISCUSSION

In our analysis of individual-level, nationally representative data capturing nursing home resident care, we found that nearly 17% of residents with persistent pain were prescribed no analgesics. This figure is quite large, given that these residents had moderate-to-severe daily pain over at least a 3-month period. We also found that more vulnerable residents within nursing homes, particularly the oldest-old and most cognitively impaired are less likely to receive prescription analgesics for this substantial, ongoing pain. These findings from a national nursing home population in 2008, nearly a decade after the groundbreaking IOM report, reinforce the IOM concerns with pain neglect and care disparities in nursing homes.

### *Persistent Pain and Analgesic Use*

Our findings that nearly 60% of eligible residents experienced some degree of pain, and that nearly 4% of residents had persistent pain, are consistent with prior studies assessing pain prevalence using the MDS. These studies, depending on the specific pain definition, have identified pain prevalence in nursing home residents ranging between 4 to 64%.<sup>6</sup> Our 4% prevalence finding is lower than most studies because we used a higher pain intensity threshold (i.e. moderate-to-severe daily pain). One recent study found that 4.8% of nursing home residents had pain on a daily basis on two consecutive MDS assessments within 120 days.<sup>5</sup>

We also found that 16.7% of the residents in our study population did not receive any prescription analgesics (i.e., opioid, NSAID, and/or acetaminophen). This figure is

lower than the estimate of no analgesic use for pain in prior studies. A study in nursing homes in 4 states from 1992-1995 found that approximately 25% of residents with any daily non-cancer pain (in one MDS assessment) did not receive any analgesics.<sup>11</sup> Another study in nursing homes in 13 states from 1998-2000 found that approximately 25% of residents with any non-cancer pain (in two out of three quarterly MDS assessments) did not receive analgesics.<sup>2</sup> Finally, a study in 185 nursing homes (predominantly in a for-profit chain) from 2007-2009 found that approximately 23% of residents with any non-cancer pain (in two consecutive MDS assessments) did not receive analgesics.<sup>26</sup> A greater percentage of our study population may have received prescription analgesics (83.3% compared to 75-77% in the other three studies) because their pain levels were more intense with our focus on persistent pain (i.e., only including moderate or severe daily pain rather than *any* daily pain). Because these residents experienced daily moderate-to-severe pain over a longer duration (e.g., at least two consecutive MDS assessments at least 90 days apart), the lack of any analgesic prescribing for nearly 17% of these residents with persistent pain is concerning.

#### *Guidelines for Persistent Pain and Analgesic Use*

An important principle for our study is that these residents should have been provided a prescription analgesic at the time of persistent pain onset under our definition (i.e. their subsequent MDS assessment with daily moderate-to-severe pain). Geriatric and nursing home practice guidelines support this principle by recommending the use of prescription analgesics, in addition to OTC drugs and non-pharmacological therapies, for persistent non-cancer pain.<sup>7,27,28</sup> The American Geriatrics Society guideline recommends acetaminophen (typically found in over-the-counter medicines) as a first-line therapy for



pain, although cautions against maximum doses in the elderly because of potential hepatotoxicity.<sup>7</sup> In our study population, this first-line approach might have been appropriate at the initial onset of a resident's pain (i.e., first MDS assessment with daily, moderate-to-severe pain). By the time a resident experienced this intense pain continuously for at least 3 months under our persistent pain definition (i.e., subsequent MDS assessments with daily, moderate-to-severe pain), prescription analgesics would be appropriate under the guidelines.

For persistent non-cancer pain that cannot be alleviated by acetaminophen, the guidelines recommend an NSAID or opioid prescription drug, but caution against long-term use of NSAIDs because of the potential for gastrointestinal bleeding and cardiovascular risks and note the need for additional studies on long-term safety and effectiveness of opioid use for persistent non-cancer pain.<sup>7,27,28</sup> A recent systematic review concluded that prescription opioids are “reasonable in the older patient with pain that has not responded to other treatments or when significant pain-related functional impairments are present despite treatment,” but cautioned that some studies have found opioids for persistent non-cancer pain to be associated with falls and hospitalizations in the elderly.<sup>29</sup> One study in the nursing home setting, though, found that opioids were safe and effective for persistent non-cancer pain.<sup>30</sup> Importantly, opioid addiction is not a significant risk in the nursing home population.<sup>7</sup> For all of these reasons, the guidelines emphasize the need for careful dose selection, close monitoring of patients, and frequent reassessment of all analgesics for persistent pain.<sup>7,27,28</sup>

### *Alternative Therapies*

It is important to consider if these residents not receiving prescription analgesics might have received instead other forms of therapy for their pain. Non-pharmacological therapies in nursing homes are also important for pain management.<sup>7,31-33</sup> However, we found only 10% of residents in persistent pain without analgesic prescribing received any physical therapy, although 20% of our study population were excluded from this calculation because their physical therapy status was not recorded on the most recent MDS assessment (Table 2.3). The percentages of these residents who received other drugs that might be prescribed for pain (e.g., muscle relaxant, oral steroid, gabapentin) were similarly low (Table 2.3).

### *Factors Associated with No Analgesic Prescribing*

Our study of nursing home residents with persistent pain identified important factors associated with no analgesic prescribing, including increasing age, greater cognitive impairment, being Black or Asian, paying for nursing home expenses on their own (“self-pay”), and being a high school or college graduate. These effects remained even after adjustment for potential confounders: number of ADL’s requiring help, MDS mood score, presence of family support, and facility compliance with federal law. We found this effect increased steadily with the increasing categories of age and cognitive impairment. The strongest effect we identified, with an approximate doubling in the odds for no analgesic prescribing, was for those residents with oldest age ( $\geq 95$  years) and moderate-severe cognitive impairment.

These associations for increasing age, greater cognitive impairment, and non-white race are consistent with our hypothesis that residents with these factors would be

less likely to receive analgesic prescriptions for persistent pain. Prior studies have also found that increasing age, cognitive impairment, and non-white race are associated with no analgesic prescribing for those residents with non-cancer pain<sup>11,26</sup> and cancer pain.<sup>15</sup> Our study expands these findings to a national nursing home population with persistent non-cancer pain. These conclusions raise important concerns about disparities in treatment for more vulnerable subpopulations within nursing homes.

Our finding that residents with greater socioeconomic status (i.e. resident self-pay and college/graduate school education) also have greater odds for not receiving prescription analgesics is the opposite conclusion from our hypothesis. This result may indicate that residents who cannot pay for nursing home charges on their own, but instead receive formal assistance (such as through Medicaid), may receive better pain management care, but this possible explanation must be explored further. In addition, a nursing home resident's education level may be less helpful for actual care in the nursing home, after controlling for family support.

For facility characteristics, the increasing proportion of self-pay residents (for the 10-30% and 30-50% categories) was statistically significantly associated with lesser odds for no analgesic prescribing (i.e., equivalent to a greater odds for prescribing), which was consistent with our hypothesis for this factor. This is consistent with a prior study's conclusion that nursing home facilities with less than 10% private pay residents (and greater than 85% Medicaid residents) had poorer quality of care (measured by health deficiencies).<sup>34</sup>

In addition, consistent with our hypothesis, there appears to be an association between increasing staff hours per resident and greater analgesic prescribing (i.e., odds

decrease for no analgesic prescribing), which peaks at the 3.5-4.0 staff hours per resident level. A recent systematic review, though, cautioned against an overemphasis on staff numbers for the quality of care in nursing homes because of the importance of other staffing factors, such as staff turnover rates.<sup>35</sup> Despite our hypothesis, we did not find any statistically significant association between for-profit status and analgesic prescribing.

Interestingly, although treated as a confounder in our model, an increase in the number of mood indicators in a resident was statistically significantly associated with lower odds (nearly half for the category with most mood indicators) for no analgesic prescribing (i.e., equivalent to greater odds for analgesic prescribing). This was consistent with the findings from another recent study<sup>26</sup> and may indicate that residents with greater mood distress (e.g., verbal expression of distress, crying, tearfulness, repetitive health complaints) are more likely to receive staff attention for pain medicine prescribing. This result may indicate that residents with less apparent distress are less likely to receive analgesic therapy, despite having persistent pain. We also found that being male was associated with greater odds for no analgesic prescribing, which appears to be a new finding, although we did not include this relationship in our hypotheses.

### *Implications*

A critical question is how nursing homes can utilize our findings and consider modifying or adopting new practices and policies to help ensure that elderly residents with persistent non-cancer pain are receiving adequate treatment. Many recent efforts have focused on improving the quality of pain care in nursing homes and emphasized the importance of multimodal approaches incorporating better pain assessment methods, improved communication between staff and clinicians, provision of pharmacological and

non-pharmacological treatments, and training and education for all of these steps.<sup>31,36,37</sup>

For example, one initiative in 49 long-term care facilities increased the percentage of residents in pain receiving analgesics from 83 percent (similar to the percentage found in our study) to 90 percent.<sup>37</sup> In addition, these efforts should ensure that more vulnerable subpopulations within nursing homes (e.g., more cognitively impaired, older, and non-white residents), as well as residents who are male or have fewer mood symptoms, are not overlooked.

### *Strengths and Limitations*

Our study has important strengths, particularly the generalizability of the results, because our study population is drawn from all nursing home residents in the United States. In addition, our measures are based on comprehensive nursing home (MDS and OSCAR) and prescribing (Part D) data. Importantly, we have addressed essential research needs identified by the IOM to estimate the extent of analgesic prescribing for nursing home residents in persistent pain and identify specific subpopulations that are less likely to receive analgesics. We were able to examine both individual and facility level factors, including SES, and control for potential confounders, including whether residents had family support and whether the facility was in compliance with federal law. Our study results confirm and expand upon prior research findings. These results were similar in our sensitivity analysis using a stricter definition of persistent pain.

The study also has important limitations. Because the MDS 2.0 measures are used by the federal government to assess nursing home quality, it is possible that measures associated with poorer quality care (particularly pain) may be underreported.<sup>38</sup> This potential weakness might mean some residents with persistent pain were

inappropriately excluded from the study population. In addition, the time lag between MDS measurements did not allow us to identify pain status on a more frequent basis within the 90-day period. Nursing home MDS assessors may also fail to measure pain accurately. To address any misclassification for persistent pain status (and study inclusion), we used alternative definitions in our sensitivity analysis and found similar results. We also did not incorporate data about over-the-counter analgesic use. Under current guidelines, though, over-the-counter analgesics would likely not be sufficient for those residents at the time of persistent pain onset (i.e., their subsequent consecutive MDS assessment with moderate-to-severe daily pain).<sup>7</sup> Finally, we did not assess the dosing of prescription analgesics or other concomitant medication use to determine if the analgesic prescription was appropriate under the guidelines.

## **CONCLUSION**

Our findings, from a study population drawn from all nursing home residents in the United States, indicate that a large proportion of nursing home residents with persistent pain are not receiving needed prescription analgesic therapy. In addition, certain resident factors (i.e., being male, older, more cognitively impaired, Black or Asian, and higher SES) are associated with lower analgesic prescribing rates. These results support the need for ongoing efforts by nursing homes to improve analgesic prescribing for residents in persistent pain, as well as additional steps to focus on these more neglected subpopulations.

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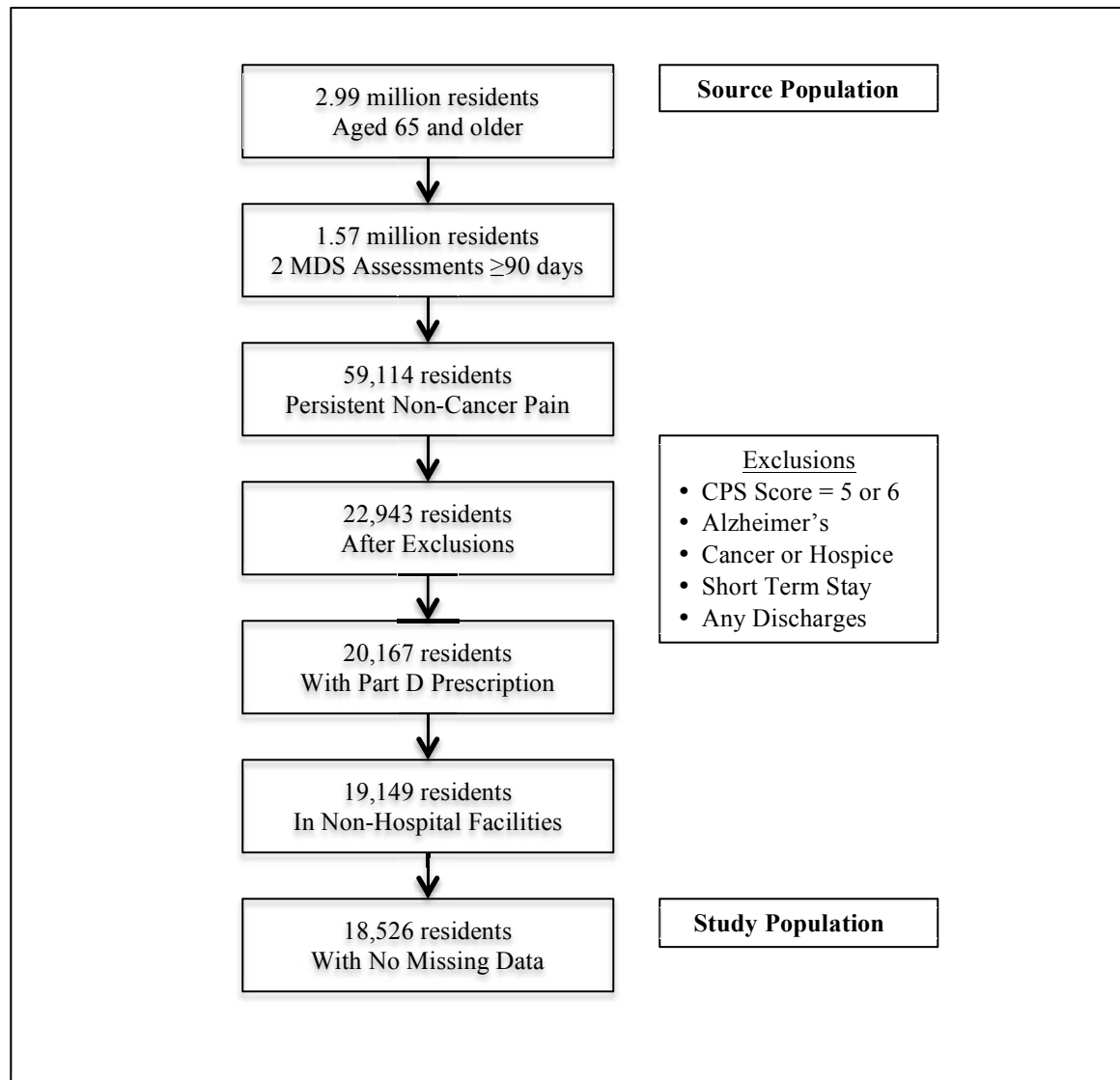


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## Figures and Tables

**Figure 2.1. Source and Study Populations from Minimum Data Set (2008).**

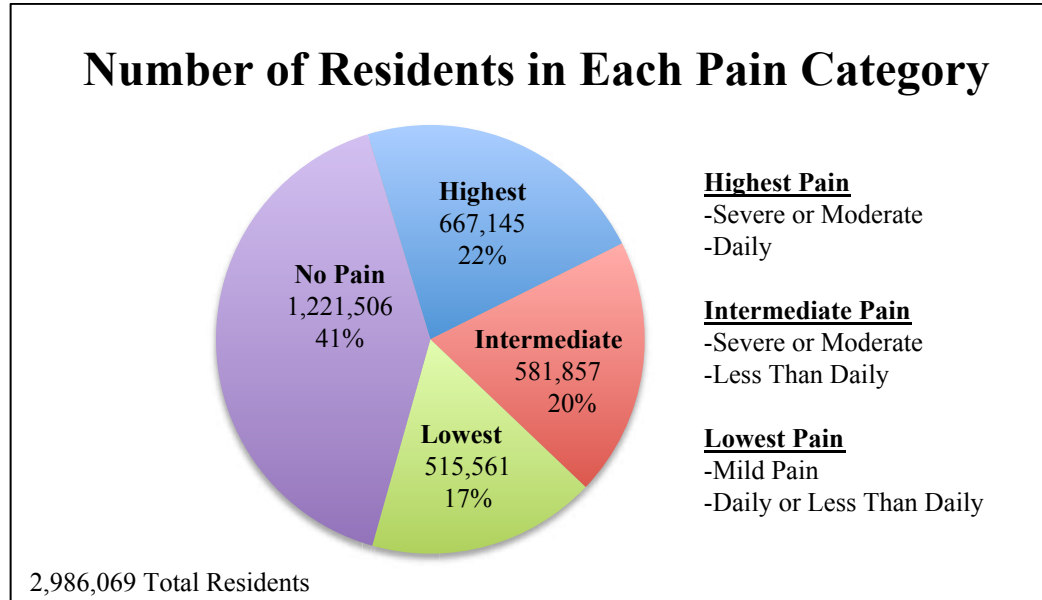


**Figure 2.2. Prescription Analgesics Used in Nursing Homes in 2008.**

<u><b>Opioids (Mu Agonist)</b></u>	<u><b>NSAIDS (Non-Selective)*</b></u>	<u><b>Acetaminophen</b></u>
Codeine	Aspirin	Acetaminophen
Fentanyl	Diclofenac	Combinations with
Hydrocodone	Diflunisal	Opioids, NSAIDs
Hydromorphone	Etodolac	
Levorphanol	Fenoprofen	
Meperidine	Flurbiprofen	
Methadone	Ibuprofen	
Morphine	Indomethacin	
Oxycodone	Ketoprofen	
Oxymorphone	Ketorolac	
Propoxyphene	Meloxicam	
	Nabumetone	
<u><b>Opioids (Dual Mechanism)</b></u>	Naproxen	
Tramadol	Oxaprozin	
	Piroxicam	
	Sulindac	
	Tolmetin	
	<u><b>NSAIDS (COX-2 Selective)*</b></u>	
	Celecoxib	

\* NSAID=Non-Steroidal Anti-Inflammatory Drug

**Figure 2.3. Pain in Source Population. Measured on At Least 1 MDS Assessment.**



**Table 2.1. Analgesics Prescribed for Study Population with Persistent Pain (n=18,526)**

<b>Analgesic Drug</b>	<b>Number (Percentage)*</b>
Prescription Opioid Combinations	14,947 (80.7%)
• Opioid Only	3,002 (16.2%)
• Opioid and Acetaminophen	9,813 (53.0%)
• Opioid and NSAID	49 (2.7%)
• Opioid, Acetaminophen, and NSAID	1,639 (8.9%)
Prescription NSAID Only	485 (2.6%)
No Prescription Analgesic	3,094 (16.7%)

\* Percentages calculated for whole study population

**Table 2.2. Characteristics in Model of Nursing Home Residents in Persistent Pain in 2008 by Analgesic Prescribing (n=18,526)\***

	<b>Received Prescription Opioid or NSAID N (%)**</b>	<b>Did Not Receive Prescription Opioid or NSAID N (%)**</b>	<b><math>\chi^2</math> Statistic p Value***</b>
<b>Total Population</b>	15,432 (83.3%)	3,094 (16.7%)	
<b>Characteristics</b>			
Gender			<0.001
Female	12,659 (82.0)	2,422 (78.3)	
Male	2,773 (18.0)	672 (21.7)	
Age			<0.001
65-74	3,787 (24.5)	564 (17.7)	
75-84	5,791 (37.5)	1,076 (34.8)	
85-94	5,057 (32.8)	1,219 (39.4)	
≥95	797 (5.2)	253 (8.2)	
Race			<0.001
White	13,415 (87.0)	2,599 (84.0)	
Black	1,367 (8.9)	337 (10.9)	
Hispanic	493 (3.2)	115 (3.7)	
Asian	76 (0.5)	31 (1.0)	
Other	81 (0.5)	12 (0.4)	
Cognitive Impairment by CPS Score			<0.001
Intact=0	4,317 (28.0)	652 (21.1)	
Borderline	3,141 (20.4)	523 (16.9)	
Intact=1			
Mild	3,427 (22.2)	731 (23.6)	
Impairment=2			
Moderate	3,984 (25.8)	994 (32.1)	
Impairment=3			
Moderate-Severe	563 (3.7)	194 (6.3)	
Impairment=4			
Resident Self-Pay			<0.001
No	13,720 (88.9)	2,586 (83.6)	
Yes	1,712 (11.1)	508 (16.4)	
Education Level			0.152
<High School Graduate	5,909 (38.3)	1,145 (37.0)	
High School Graduate	8,586 (55.6)	1,737 (56.1)	
College Graduate	937 (6.1)	212 (6.9)	

Staff Hours Per Resident			0.001
<2.5 Hours	1,713 (7.6)	308 (10.0)	
2.5-3.0 Hours	2,597 (16.8)	523 (16.9)	
3.0-3.5 Hours	4,473 (29.0)	882 (28.5)	
3.5-4.0 Hours	3,772 (24.4)	712 (23.0)	
4.0-4.5 Hours	2,047 (13.3)	391 (12.6)	
>4.5 Hours	1,370 (8.9)	278 (9.0)	
Facility's Proportion of Residents Self-Pay			<0.001
<10%	2,799 (18.1)	624 (20.2)	
10-30%	8,957 (58.0)	1,665 (53.8)	
30-50%	2,931 (19.0)	599 (19.4)	
>50%	745 (4.8)	206 (6.7)	
Facility For Profit			<0.001
No	4,310 (27.9)	976 (31.5)	
Yes	11,122 (72.1)	2,118 (68.5)	
ADL Help: Morris Additive Scale			<0.001
0 ADLs	1,291 (8.4)	206 (6.7)	
1-7 ADLs	2,972 (19.3)	521 (16.8)	
8-14 ADLs	3,482 (22.6)	690 (22.3)	
15-21 ADLs	5,396 (35.0)	1,129 (36.5)	
22-28 ADLs	2,291 (14.9)	548 (17.7)	
MDS Mood Scale			<0.001
0	7,568 (49.0)	1,669 (53.9)	
1-2	3,829 (24.8)	751 (24.3)	
3-4	2,847 (18.5)	473 (15.3)	
5-6	1,043 (6.8)	178 (5.8)	
7-8	145 (0.9)	23 (0.7)	
Family Support			<0.001
No	8,652 (56.1)	1,603 (51.8)	
Yes	6,780 (43.9)	1,491 (48.2)	
Facility Compliant with Federal Law			0.817
Yes	13,644 (88.4)	2,731 (88.3)	
No	1,788 (11.6)	363 (11.7)	

Notes: Due to rounding, percentages do not all sum to 100. NSAID=Non-Steroidal Anti-Inflammatory Drug. ADL=Activities of Daily Living. CPS=Cognitive Performance Scale.

\* Excludes 623 (3.3%) observations with missing values.

\*\* All percentages correspond to row totals.

\*\*\* p value corresponds to the  $X^2$  statistic.



**Table 2.3. Additional Treatments or Medications for Nursing Home Residents in Persistent Pain in 2008 by Analgesic Prescribing (n=18,526)\***

	<b>Received Prescription Opioid or NSAID N (%)**</b>	<b>Did Not Receive Prescription Opioid or NSAID N (%)**</b>	<b>X<sup>2</sup> Statistic p Value***</b>
<b>Total Population</b>	15,432 (83.3%)	3,094 (16.7%)	
<b>Treatments</b>			
Muscle Relaxant			<0.001
No	14,034 (90.9)	2,972 (96.1)	
Yes	1,398 (9.1)	122 (3.9)	
Steroid			<0.001
No	13,856 (89.8)	2,917 (94.3)	
Yes	1,576 (10.2)	177 (5.7)	
Gabapentin			<0.001
No	12,222 (79.2)	2,770 (89.5)	
Yes	3,210 (20.8)	324 (10.5)	
Anti-Depressant			<0.001
No	4,806 (31.1)	1,591 (51.4)	
Yes	10,626 (68.9)	1,503 (48.6)	
Anti-Psychotic			0.065
No	12,320 (79.8)	2,515 (81.3)	
Yes	3,112 (20.2)	579 (18.7)	
Mood Stabilizing/Anti-Convulsant			<0.001
No	11,222 (72.7)	2,607 (84.3)	
Yes	4,210 (27.3)	487 (15.7)	
Anti-Anxiety			<0.001
No	14,857 (96.3)	3,030 (97.9)	
Yes	575 (3.7)	64 (2.1)	
Physical Therapy (at least 1 day)****			0.271
No	11,318 (92.0)	2,338 (91.4)	
Yes	982 (8.0)	221 (8.6)	

*Notes:* Due to rounding, percentages do not all sum to 100. NSAID=Non-Steroidal Anti-Inflammatory Drug. ADL=Activities of Daily Living. CPS=Cognitive Performance Scale.

\* Excludes 623 (3.3%) observations with missing values.

\*\* All percentages correspond to row totals.

\*\*\* p value corresponds to the X<sup>2</sup> statistic.

\*\*\*\* Excluded 3,667 (19.8%) additional observations without physical therapy recorded.

**Table 2.4. Odds Ratios for Not Receiving a Prescription Pain Medicine.**

	Univariate Models* (n=18,526)			Multivariate Model** (n=18,526)		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	<b>1.30</b>	<b>1.17-1.44</b>	<b>&lt;0.001</b>	<b>1.38</b>	<b>1.24-1.53</b>	<b>&lt;0.001</b>
Age						
65-74	(Ref)			(Ref)		
75-84	<b>1.29</b>	<b>1.16-1.46</b>	<b>&lt;0.001</b>	<b>1.30</b>	<b>1.16-1.47</b>	<b>&lt;0.001</b>
85-94	<b>1.66</b>	<b>1.48-1.87</b>	<b>&lt;0.001</b>	<b>1.63</b>	<b>1.44-1.85</b>	<b>&lt;0.001</b>
≥95	<b>2.18</b>	<b>1.82-2.61</b>	<b>&lt;0.001</b>	<b>2.06</b>	<b>1.70-2.49</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	<b>1.25</b>	<b>1.09-1.45</b>	<b>0.002</b>	<b>1.20</b>	<b>1.03-1.39</b>	<b>0.017</b>
Hispanic	1.10	0.87-1.38	0.444	1.07	0.84-1.35	0.600
Asian	<b>2.18</b>	<b>1.35-3.53</b>	<b>0.002</b>	<b>1.97</b>	<b>1.22-3.20</b>	<b>0.006</b>
Other	0.85	0.44-1.63	0.623	0.94	0.48-1.82	0.854
<b>Cognitive Impairment by CPS Score</b>						
Intact=0	(Ref)			(Ref)		
Borderline	1.09	0.96-1.25	0.181	1.11	0.97-1.27	0.120
Intact=1						
Mild	<b>1.37</b>	<b>1.21-1.55</b>	<b>&lt;0.001</b>	<b>1.31</b>	<b>1.15-1.49</b>	<b>&lt;0.001</b>
Impairment=2						
Moderate	<b>1.66</b>	<b>1.48-1.87</b>	<b>&lt;0.001</b>	<b>1.61</b>	<b>1.42-1.83</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-	<b>2.29</b>	<b>1.87-2.79</b>	<b>&lt;0.001</b>	<b>2.12</b>	<b>1.71-2.62</b>	<b>&lt;0.001</b>
Severe						
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>1.52</b>	<b>1.35-1.72</b>	<b>&lt;0.001</b>	<b>1.40</b>	<b>1.23-1.59</b>	<b>&lt;0.001</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.03	0.94-1.12	0.551	<b>1.10</b>	<b>1.01-1.21</b>	<b>0.035</b>
Graduate						
College	1.18	0.99-1.41	0.060	<b>1.22</b>	<b>1.02-1.46</b>	<b>0.029</b>
Graduate						

Univariate Models (continued)				Multivariate Model (continued)		
Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	<b>0.82</b>	<b>0.68-0.99</b>	<b>0.040</b>	<b>0.80</b>	<b>0.67-0.98</b>	<b>0.027</b>
3.0-3.5 Hours	0.85	0.71-1.02	0.087	<b>0.83</b>	<b>0.69-0.99</b>	<b>0.044</b>
3.5-4.0 Hours	0.85	0.70-1.02	0.084	<b>0.80</b>	<b>0.66-0.97</b>	<b>0.021</b>
4.0-4.5 Hours	0.89	0.72-1.10	0.290	0.81	0.66-1.01	0.061
>4.5 Hours	0.92	0.73-1.16	0.479	0.81	0.64-1.02	0.073
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	<b>0.82</b>	<b>0.72-0.92</b>	<b>0.001</b>	<b>0.80</b>	<b>0.71-0.91</b>	<b>0.001</b>
30-50%	<b>0.85</b>	<b>0.73-0.99</b>	<b>0.040</b>	<b>0.77</b>	<b>0.66-0.91</b>	<b>0.002</b>
>50%	1.16	0.93-1.45	0.179	0.91	0.72-1.16	0.454
Facility For Profit						
No	(Ref)					
Yes	<b>0.87</b>	<b>0.78-0.97</b>	<b>0.009</b>	0.91	0.81-1.01	0.078
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.09	0.91-1.31	0.357	1.00	0.83-1.20	0.980
8-14 ADLs	<b>1.27</b>	<b>1.06-1.52</b>	<b>0.009</b>	1.11	0.92-1.33	0.285
15-21 ADLs	<b>1.36</b>	<b>1.14-1.62</b>	<b>0.001</b>	1.15	0.96-1.37	0.130
22-28 ADLs	<b>1.56</b>	<b>1.30-1.89</b>	<b>&lt;0.001</b>	1.21	0.99-1.47	0.059
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	<b>0.85</b>	<b>0.77-0.95</b>	<b>0.003</b>	<b>0.82</b>	<b>0.74-0.91</b>	<b>&lt;0.001</b>
3-4	<b>0.72</b>	<b>0.64-0.81</b>	<b>&lt;0.001</b>	<b>0.67</b>	<b>0.59-0.76</b>	<b>&lt;0.001</b>
5-6	<b>0.70</b>	<b>0.58-0.84</b>	<b>&lt;0.001</b>	<b>0.61</b>	<b>0.51-0.74</b>	<b>&lt;0.001</b>
7-8	0.65	0.40-1.04	0.069	<b>0.52</b>	<b>0.32-0.83</b>	<b>0.007</b>
Family Support						
No	(Ref)			(Ref)		
Yes	<b>1.17</b>	<b>1.07-1.27</b>	<b>&lt;0.001</b>	<b>1.09</b>	<b>1.00-1.19</b>	<b>0.042</b>
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	1.01	0.87-1.17	0.870	1.00	0.86-1.16	0.977

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Univariate Logistic Models. This column presents the univariate logistic model results for each individual variable, unadjusted for the other variables.

\*\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; and facility compliance with federal law.

All regressions used multi-level modeling at the state and facility levels.

**Appendix S2.A. Sensitivity Analyses: Vary Definition of “Persistent Pain” in Multivariate Models.\* Odds Ratios for Not Receiving a Prescription Pain Medicine.**

	<b>Model 1: At least 3 consecutive visits at least 90-180 days apart (n=10,568)</b>			<b>Model 2: At least 2 consecutive visits at least 90-120 days apart (n=10,811)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	<b>1.43</b>	<b>1.24-1.65</b>	<b>&lt;0.001</b>	<b>1.36</b>	<b>1.18-1.57</b>	<b>&lt;0.001</b>
Age						
65-74	(Ref)			(Ref)		
75-84	<b>1.44</b>	<b>1.23-1.70</b>	<b>&lt;0.001</b>	<b>1.21</b>	<b>1.02-1.42</b>	<b>0.026</b>
85-94	<b>1.80</b>	<b>1.52-2.13</b>	<b>&lt;0.001</b>	<b>1.54</b>	<b>1.30-1.83</b>	<b>&lt;0.001</b>
≥95	<b>2.00</b>	<b>1.52-2.62</b>	<b>&lt;0.001</b>	<b>2.08</b>	<b>1.63-2.68</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	<b>1.41</b>	<b>1.16-1.71</b>	<b>0.001</b>	1.05	0.86-1.29	0.639
Hispanic	1.05	0.75-1.48	0.777	1.15	0.85-1.56	0.350
Asian	<b>2.20</b>	<b>1.06-4.55</b>	<b>0.035</b>	1.78	0.95-3.33	0.070
Other	0.61	0.20-1.84	0.383	1.14	0.50-2.59	0.749
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.11	0.93-1.32	0.258	1.13	0.94-1.36	0.189
Intact=1						
Mild	<b>1.24</b>	<b>1.05-1.48</b>	<b>0.014</b>	<b>1.43</b>	<b>1.20-1.70</b>	<b>&lt;0.001</b>
Impairment=2						
Moderate	<b>1.61</b>	<b>1.36-1.91</b>	<b>&lt;0.001</b>	<b>1.67</b>	<b>1.41-1.99</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>2.01</b>	<b>1.50-2.70</b>	<b>&lt;0.001</b>	<b>2.24</b>	<b>1.69-2.98</b>	<b>&lt;0.001</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>1.41</b>	<b>1.18-1.67</b>	<b>&lt;0.001</b>	<b>1.40</b>	<b>1.18-1.70</b>	<b>&lt;0.001</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.05	0.92-1.18	0.477	<b>1.22</b>	<b>1.08-1.38</b>	<b>0.002</b>
Graduate						
College Graduate	1.10	0.86-1.41	0.427	<b>1.39</b>	<b>1.09-1.78</b>	<b>0.008</b>

Model 1 (continued)				Model 2 (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.92	0.71-1.19	0.521	<b>0.71</b>	<b>0.56-0.90</b>	<b>0.005</b>
3.0-3.5 Hours	0.82	0.64-1.06	0.127	0.80	0.64-1.01	0.056
3.5-4.0 Hours	0.79	0.60-1.02	0.071	<b>0.75</b>	<b>0.59-0.95</b>	<b>0.018</b>
4.0-4.5 Hours	0.82	0.62-1.10	0.190	0.78	0.59-1.02	0.069
>4.5 Hours	0.85	0.61-1.16	0.300	<b>0.73</b>	<b>0.54-0.98</b>	<b>0.035</b>
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	<b>0.75</b>	<b>0.64-0.89</b>	<b>0.001</b>	<b>0.84</b>	<b>0.71-0.98</b>	<b>0.032</b>
30-50%	<b>0.74</b>	<b>0.60-0.92</b>	<b>0.006</b>	<b>0.80</b>	<b>0.64-0.98</b>	<b>0.034</b>
>50%	0.80	0.58-1.09	0.159	0.98	0.71-1.34	0.884
Facility For Profit						
No	(Ref)					
Yes	0.87	0.75-1.01	0.061	0.95	0.80-1.07	0.300
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.14	0.88-1.48	0.331	0.92	0.72-1.19	0.534
8-14 ADLs	1.18	0.91-1.52	0.215	1.00	0.78-1.28	0.995
15-21 ADLs	1.25	0.97-1.59	0.081	1.06	0.83-1.34	0.652
22-28 ADLs	<b>1.38</b>	<b>1.05-1.81</b>	<b>0.022</b>	1.09	0.84-1.42	0.523
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	<b>0.79</b>	<b>0.69-0.20</b>	<b>0.002</b>	<b>0.82</b>	<b>0.71-0.94</b>	<b>0.006</b>
3-4	<b>0.63</b>	<b>0.54-0.75</b>	<b>&lt;0.001</b>	<b>0.72</b>	<b>0.61-0.86</b>	<b>&lt;0.001</b>
5-6	<b>0.56</b>	<b>0.44-0.73</b>	<b>&lt;0.001</b>	<b>0.68</b>	<b>0.53-0.87</b>	<b>0.003</b>
7-8	0.61	0.33-1.12	0.114	<b>0.36</b>	<b>0.17-0.79</b>	<b>0.011</b>
Family Support						
No	(Ref)			(Ref)		
Yes	1.10	0.98-1.24	0.101	1.11	0.99-1.25	0.076
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.96	0.79-1.16	0.657	1.10	0.91-1.33	0.332

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; and facility compliance with federal law.

All regressions used multi-level modeling at the state and facility levels.

**Appendix S2.B. Subgroup Analysis by Disease or Condition: Four Multi-Level Models.\* Odds Ratios for Not Receiving a Prescription Pain Medicine.**

	<b>Model 1: Arthritis (n=8,589)</b>			<b>Model 2: Diabetes (n=6,403)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	<b>1.43</b>	<b>1.20-1.70</b>	<b>&lt;0.001</b>	<b>1.39</b>	<b>1.17-1.66</b>	<b>&lt;0.001</b>
Age						
65-74	(Ref)			(Ref)		
75-84	<b>1.22</b>	<b>1.00-1.49</b>	<b>0.046</b>	<b>1.34</b>	<b>1.11-1.61</b>	<b>0.002</b>
85-94	<b>1.59</b>	<b>1.30-1.94</b>	<b>&lt;0.001</b>	<b>1.56</b>	<b>1.26-1.92</b>	<b>&lt;0.001</b>
≥95	<b>2.16</b>	<b>1.64-2.87</b>	<b>&lt;0.001</b>	1.46	0.91-2.32	0.114
Race						
White	(Ref)			(Ref)		
Black	<b>1.49</b>	<b>1.20-1.86</b>	<b>&lt;0.001</b>	<b>1.28</b>	<b>1.03-1.60</b>	<b>0.029</b>
Hispanic	1.00	0.66-1.51	0.998	1.20	0.85-1.70	0.296
Asian	1.94	0.89-4.27	0.098	<b>3.00</b>	<b>1.48-6.09</b>	<b>0.002</b>
Other	1.13	0.37-3.42	0.827	1.45	0.62-3.44	0.394
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	0.95	0.77-1.16	0.620	1.09	0.87-1.37	0.450
Intact=1						
Mild	1.13	0.93-1.37	0.219	<b>1.36</b>	<b>1.09-1.70</b>	<b>0.006</b>
Impairment=2						
Moderate	<b>1.53</b>	<b>1.27-1.85</b>	<b>&lt;0.001</b>	<b>1.55</b>	<b>1.25-1.93</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>1.70</b>	<b>1.20-2.39</b>	<b>0.003</b>	<b>2.40</b>	<b>1.64-3.51</b>	<b>&lt;0.001</b>
Severe						
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>1.44</b>	<b>1.19-1.74</b>	<b>&lt;0.001</b>	<b>1.58</b>	<b>1.24-2.03</b>	<b>&lt;0.001</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.08	0.94-1.24	0.261	1.03	0.88-1.20	0.723
Graduate						
College	1.21	0.92-1.59	0.166	1.04	0.74-1.45	0.836
Graduate						

Model 1: Arthritis (continued)				Model 2: Diabetes (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.89	0.67-1.19	0.427	<b>0.69</b>	<b>0.50-0.95</b>	<b>0.024</b>
3.0-3.5 Hours	1.03	0.78-1.35	0.832	0.88	0.65-1.18	0.390
3.5-4.0 Hours	0.95	0.71-1.26	0.704	0.92	0.67-1.27	0.626
4.0-4.5 Hours	0.99	0.73-1.36	0.966	0.83	0.58-1.18	0.300
>4.5 Hours	1.02	0.73-1.43	0.909	0.85	0.58-1.25	0.419
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	<b>0.81</b>	<b>0.67-0.97</b>	<b>0.019</b>	0.86	0.70-1.05	0.130
30-50%	<b>0.77</b>	<b>0.61-0.97</b>	<b>0.024</b>	0.80	0.61-1.04	0.097
>50%	0.90	0.64-1.26	0.530	1.05	0.69-1.61	0.808
Facility For Profit						
No	(Ref)					
Yes	<b>0.82</b>	<b>0.70-0.96</b>	<b>0.012</b>	0.86	0.72-1.04	0.114
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.04	0.78-1.40	0.663	0.96	0.68-1.34	0.775
8-14 ADLs	1.12	0.84-1.49	0.446	1.15	0.83-1.60	0.394
15-21 ADLs	1.18	0.90-1.56	0.102	1.08	0.79-1.47	0.650
22-28 ADLs	1.29	0.95-1.76	0.058	1.14	0.81-1.61	0.459
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.85	0.73-1.00	0.051	<b>0.78</b>	<b>0.65-0.94</b>	<b>0.010</b>
3-4	<b>0.66</b>	<b>0.55-0.80</b>	<b>&lt;0.001</b>	<b>0.66</b>	<b>0.53-0.82</b>	<b>&lt;0.001</b>
5-6	<b>0.63</b>	<b>0.49-0.83</b>	<b>0.001</b>	<b>0.51</b>	<b>0.36-0.73</b>	<b>&lt;0.001</b>
7-8	0.57	0.30-1.07	0.079	0.66	0.29-1.52	0.333
Family Support						
No	(Ref)			(Ref)		
Yes	0.98	0.86-1.12	0.810	1.09	0.93-1.27	0.276
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.89	0.72-1.10	0.279	1.12	0.88-1.41	0.357

Model 3: Back Pain (n=2,141)				Model 4: Osteoporosis (n=4,818)		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	<b>1.53</b>	<b>1.06-2.22</b>	<b>0.023</b>	<b>1.51</b>	<b>1.09-2.09</b>	<b>0.014</b>
Age						
65-74	(Ref)			(Ref)		
75-84	1.08	0.72-1.62	0.719	1.11	0.84-1.48	0.457
85-94	1.50	0.99-2.29	0.057	<b>1.47</b>	<b>1.11-1.95</b>	<b>0.006</b>
≥95	<b>2.29</b>	<b>1.24-4.22</b>	<b>0.008</b>	<b>2.50</b>	<b>1.72-3.66</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	0.93	0.47-1.83	0.823	1.13	0.76-1.69	0.545
Hispanic	1.70	0.74-3.90	0.209	1.37	0.81-2.32	0.238
Asian	<b>7.30</b>	<b>1.34-39.72</b>	<b>0.021</b>	1.99	0.86-4.60	0.108
Other	2.92	0.27-32.02	0.381	1.07	0.28-4.10	0.916
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	<b>1.91</b>	<b>1.21-3.00</b>	<b>0.005</b>	1.22	0.91-1.63	0.178
Intact=1						
Mild	1.40	0.89-2.19	0.142	<b>1.33</b>	<b>1.02-1.75</b>	<b>0.038</b>
Impairment=2						
Moderate	<b>2.03</b>	<b>1.30-3.15</b>	<b>0.002</b>	<b>1.70</b>	<b>1.30-2.22</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>2.37</b>	<b>1.04-5.40</b>	<b>0.040</b>	<b>1.96</b>	<b>1.23-3.12</b>	<b>0.005</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>1.58</b>	<b>1.07-2.34</b>	<b>0.022</b>	<b>1.34</b>	<b>1.04-1.73</b>	<b>0.022</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School Graduate	<b>1.56</b>	<b>1.13-2.15</b>	<b>0.006</b>	0.99	0.82-1.21	0.954
College Graduate	1.57	0.86-2.88	0.142	1.17	0.82-1.69	0.387
Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.80	0.48-1.34	0.401	<b>0.65</b>	<b>0.44-0.96</b>	<b>0.032</b>
3.0-3.5 Hours	0.67	0.40-1.10	0.116	0.80	0.56-1.14	0.215
3.5-4.0 Hours	<b>0.51</b>	<b>0.30-0.88</b>	<b>0.015</b>	<b>0.62</b>	<b>0.42-0.91</b>	<b>0.015</b>
4.0-4.5 Hours	<b>0.51</b>	<b>0.27-0.96</b>	<b>0.038</b>	0.88	0.58-1.33	0.551
>4.5 Hours	<b>0.36</b>	<b>0.17-0.76</b>	<b>0.007</b>	0.78	0.50-1.22	0.272



Model 3: Back Pain (continued)				Model 4: Osteoporosis (continued)		
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	0.80	0.53-1.22	0.302	0.82	0.64-1.07	0.142
30-50%	0.63	0.38-1.04	0.069	0.74	0.54-1.01	0.060
>50%	0.88	0.43-1.79	0.731	1.25	0.82-1.91	0.299
Facility For Profit						
No	(Ref)					
Yes	0.71	0.50-1.01	0.057	0.99	0.80-1.23	0.919
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.64	0.89-3.03	0.112	0.86	0.57-1.29	0.463
8-14 ADLs	1.10	0.59-2.07	0.759	1.06	0.72-1.56	0.766
15-21 ADLs	<b>2.03</b>	<b>1.13-3.66</b>	<b>0.018</b>	1.20	0.83-1.75	0.329
22-28 ADLs	1.85	0.94-3.66	0.077	1.15	0.75-1.76	0.520
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.82	0.59-1.16	0.266	0.83	0.67-1.03	0.089
3-4	<b>0.60</b>	<b>0.39-0.91</b>	<b>0.016</b>	<b>0.63</b>	<b>0.49-0.82</b>	<b>0.001</b>
5-6	<b>0.35</b>	<b>0.20-0.63</b>	<b>&lt;0.001</b>	0.71	0.50-1.01	0.057
7-8	0.72	0.29-1.80	0.483	0.60	0.25-1.44	0.253
Family Support						
No	(Ref)			(Ref)		
Yes	1.21	0.90-1.62	0.206	1.04	0.87-1.25	0.646
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	1.13	0.73-1.74	0.594	1.18	0.90-1.56	0.229

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; and facility compliance with federal law.

All regressions used multi-level modeling at the state and facility levels.

**CHAPTER 3: INAPPROPRIATE FENTANYL  
PRESCRIBING AMONG NURSING HOME RESIDENTS IN  
THE UNITED STATES**

## **Abstract**

Objective: FDA has warned that transdermal fentanyl should be limited to individuals with prior opioid use and persistent pain. Our objective was to quantify the prevalence of transdermal fentanyl prescribing in elderly nursing home residents without prior opioid use or persistent pain and the association of individual and facility traits with opioid-naïve prescribing.

Design: Cross-sectional study.

Setting: Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims.

Participants: From a cross-section of all long-stay U.S. nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified individuals ( $\geq 65$  years old) who initiated transdermal fentanyl, excluding those with Alzheimer's, severe cognitive impairment, cancer or receipt of hospice care.

Measurements: We used Medicare Part D to select beneficiaries initiating transdermal fentanyl in 2008 and examined whether they were "opioid-naïve," defined as no opioid prescriptions during the previous 60 days. We obtained resident and facility characteristics from MDS and OSCAR records and defined persistent pain as moderate-to-severe, daily pain on consecutive MDS assessments at least 90 days apart. We

estimated associations of patient and facility attributes and opioid-naïve fentanyl initiation using multilevel mixed effects logistic regression analyses.

Results: Among 17,052 residents who initiated transdermal fentanyl, 6,190 (36.3%) were opioid-naïve and 15,659 (91.8%) did not have persistent pain. In the regression analysis with adjustments, residents who were older (compared to those 65-74, ages 75-84 odds ratio (OR)=1.16, 95% CI=1.04-1.29; ages 85-94 OR=1.30, 95% CI 1.16-1.44; ages  $\geq$ 95 OR= 1.69, 95% CI = 1.46-1.95) or more cognitively impaired (compared to no cognitive impairment, borderline intact OR=1.06, 95% CI=0.93-1.20; mild impairment OR=1.31, 95% CI=1.16-1.47; moderate impairment OR=1.60, 95% CI=1.44-1.78; moderate-to-severe cognitive impairment, OR=1.99, 95% CI = 1.73-2.29) were more likely to initiate transdermal fentanyl without prior opioid use.

Conclusion: Most nursing home residents initiating transdermal fentanyl did not have persistent pain and many were opioid-naïve. Changes in prescribing practices may be necessary to ensure FDA warnings are followed, particularly for vulnerable subgroups such as the cognitively impaired.

## INTRODUCTION

Nursing home care is critical for the health of millions in the United States. Nearly 3 million Americans aged 65 years and older resided in a nursing home at some point in 2009, and over 1 million of these residents were 85 years and older.<sup>1</sup> More elderly will reside in nursing homes as the American population grows. Most elderly nursing home residents experience significant diseases and debilitating conditions related to older age. Nearly three-quarters of nursing home residents need assistance with at least one basic “activity of daily living” (ADL) and half need assistance with at least four ADLs.<sup>1</sup> Forty percent of nursing home residents also have a moderate or severe cognitive deficit.<sup>1</sup> Because of these qualities, nursing home residents are a vulnerable population who require special care.

Pain is a common condition for many nursing home residents, including persistent pain (typically defined as occurring over a three-month period or longer).<sup>2</sup> Prior studies have found that between 45 to 80 percent of residents experience some degree of pain that impairs functioning and quality of life<sup>3</sup> and 5 to 49 percent of residents have persistent non-cancer pain, depending on the duration and intensity threshold.<sup>2,4,5</sup> Pain in elderly nursing home residents can adversely affect their physical functioning, mental health, and social engagement, and thus severely limit their quality of life.<sup>6-8</sup> Many nursing home residents are more vulnerable to pain’s damaging effects because of their greater frailty and diminished resilience.<sup>7</sup>

Geriatric and nursing home guidelines recommend analgesics as an important option for treating resident pain, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and prescription opioids.<sup>9-11</sup> Prescription opioids in particular have been used for decades to treat brief, acute pain, as well as cancer pain.<sup>12</sup>

These guidelines also recommend prescription opioids to treat persistent non-cancer pain under some conditions but note that additional studies are needed on their long-term safety and effectiveness.<sup>9-11</sup> The elderly are particularly vulnerable to side effects from opioids.<sup>9-11</sup>

Transdermal fentanyl is a long-acting opioid commonly prescribed for nursing home residents with pain.<sup>13</sup> The U.S. Food and Drug Administration (FDA) initially approved transdermal fentanyl in 1990 for patients with moderate-to-severe, continuous pain who have been receiving opioid therapy (and are thus opioid-tolerant).<sup>14</sup> FDA established the drug's approved conditions of use, including warnings, that are specified in the drug's labeling.<sup>15</sup> Transdermal fentanyl is contraindicated in patients who do not have moderate-to-severe, continuous pain, and who are not opioid-tolerant from taking another opioid drug, such as a short-acting or other long-acting form.<sup>16</sup> Patients who have only mild or intermittent pain, or who have not received any prior opioid drug (and are thus "opioid naïve"), deviate most significantly from the FDA-approved conditions.

Inappropriate prescribing of transdermal fentanyl poses significant risks to nursing home residents. Respiratory depression in opioid-naïve patients is an important concern.<sup>15</sup> Because FDA received reports of death and life-threatening adverse events when the drug was used in patients who did not have moderate-to-severe, continuous pain or who were not opioid-tolerant, FDA communicated this risk in 2005 to the public and health care providers in a Public Health Advisory (PHA)<sup>17</sup> and Information for Health Care Professionals (IHCP).<sup>18</sup> FDA issued a second PHA<sup>19</sup> and IHCP<sup>20</sup> in December 2007 when the agency continued to receive these serious adverse event reports.

Health care providers can rely, among other things, on the drug's labeled conditions (including warnings and contraindications) and FDA's safety updates (such as the Information for Healthcare Professionals) to determine whether a nursing home resident should be prescribed an opioid drug. The guidelines for pain management in the elderly and at nursing homes emphasize that prescription opioids must be selected appropriately for each patient according to FDA-approved labeled conditions.<sup>9,10</sup> CMS guidelines emphasize that nursing homes should follow current practice standards, including the FDA-approved labeling conditions, in treating a resident's pain with medication.<sup>21</sup> In this way the practice and CMS guidelines incorporate the FDA's condition that only patients with moderate-to-severe, continuous pain, and who are opioid-tolerant, initiate transdermal fentanyl.

A critical question is whether these guidelines and FDA warnings are being followed for opioid prescribing in nursing homes. The Institute of Medicine (IOM) has expressed significant concerns with inadequate care for nursing home residents, including for pain management and inappropriate drug prescribing.<sup>12</sup> These care inadequacies may be more severe for more vulnerable subpopulations within nursing homes and at specific types of facilities. Prior studies have identified disparities in pain management for nursing home residents who are older, non-white, and cognitively impaired.<sup>8,22-24</sup> Certain facility characteristics, such as for-profit status, have also been associated with worse health outcomes for residents.<sup>25</sup>

To determine whether transdermal fentanyl prescribing in this vulnerable elderly population has complied with FDA safety communications and drug labeling indications, we assessed data on nursing home residents, facilities, and medication prescribing in

2008 from the national Minimum Data Set (MDS), the Online Survey, Certification, and Reporting (OSCAR) database, and Medicare Part D. Specifically, we evaluated the extent of transdermal fentanyl prescribing for elderly nursing home residents and determined whether residents receiving fentanyl transdermal prescriptions for the first time had moderate-to-severe, continuous pain and were not taking another opioid (opioid-naïve). We then assessed whether certain individual and facility-level factors were associated with opioid-naïve prescribing.

## METHODS

### *Participants*

Our source population was the approximately 1.4 million individuals who resided in a nursing home in the United States at any time between January 1, 2008, and December 31, 2008, and had at least one prescription drug documented in a Part D record. Approximately 81% of nursing home residents were estimated to have enrolled in the Part D program in 2006 just prior to our study period.<sup>26</sup> The Part D prescription record provides information about the drug, dose, dosage form strength, and days supply.<sup>27</sup> We also relied on MDS measurements to create our study population. All United States nursing homes are required by federal law (for Medicare and/or Medicaid certification) to use the MDS survey instrument to assess each nursing home resident periodically.<sup>28</sup>

*Inclusion Criteria.* Only those residents who received a transdermal fentanyl prescription in 2008 were eligible for our study, which narrowed the population to 101,809 residents (7.3% of the source population) (Figure 3.1). From this population, we only included residents with at least one MDS record before fentanyl initiation. We



defined fentanyl initiation as the date of a resident's first transdermal fentanyl prescription during 2008. We also defined the "duration end date" for each prescription by adding the number of days' supply to the prescription date. Only new fentanyl users were included in the study, defined as those residents who did not have an earlier transdermal fentanyl prescription with a duration end date within the two months prior to fentanyl initiation (e.g., the two-month window). In addition, only those residents who had at least one Part D prescription during this two-month prior window and who were 65 years or older were eligible for our study. Finally, we only included those residents who had a long-term stay (defined as at least 90 continuous days) prior to their transdermal fentanyl initiation. There were 32,244 eligible residents who met these criteria (Figure 3.1).

*Exclusion Criteria.* We excluded those individuals who had cancer or were terminally ill because of the distinct pain management issues faced by this patient population. We also excluded those with Alzheimer's disease or most severe cognitive impairment, defined as an MDS Cognitive Performance Scale (CPS) score of 5 or 6 (Figure 1), because of the difficulty in assessing accurately their pain levels,<sup>23</sup> which could affect analgesic prescribing. After these exclusions, 18,607 individuals remained in our study population. We then excluded 994 individuals (5.3%) who resided in hospital-based facilities, so that 18,800 individuals remained. Finally, we dropped 561 subjects who were missing data for at least one covariate in our analysis (3.2% of the sample), so that our final study population consisted of 17,052 residents (Figure 3.1).

## *Measures*

We analyzed data from the MDS about each nursing home resident initiating transdermal fentanyl. The MDS is a standardized survey instrument measuring each resident on fifteen domains, including any degree of pain, cognitive and physical functioning, psychosocial well-being, activities and diseases.<sup>29</sup> The MDS assessor, a trained nursing home staff person, relies on personal observation, interviews with residents, resident medical records, discussions with resident family, and consultation with clinicians and other staff to complete the MDS questions and record all information on the MDS forms.<sup>29,30</sup> The information gathered for the MDS is then used by the nursing home to develop individual care plans for each resident.<sup>28,30</sup> The nursing home assesses each resident every three months for certain MDS measures (including cognitive and physical functioning, mood, and pain) and annually for all MDS measures and when any significant change in resident status occurs.<sup>29</sup>

Our study relied on the MDS 2.0 version, which was used by nursing homes during our 2007-08 study period. The MDS 2.0 measures in our study have been found generally reliable and valid for the domains when used by trained staff.<sup>31</sup> For example, MDS 2.0 items have been incorporated into other valid and reliable instruments (e.g., MDS ADL Scale, MDS Cognitive Performance Scale) to measure resident characteristics, such as physical and cognitive functioning.<sup>31-33</sup> We also relied on OSCAR data for measurement of facility factors, such as the facility's staff-to-resident ratio, percentage of private pay residents, for-profit status, and compliance with federal law. The federal government compiles this nursing home facility information annually in OSCAR.<sup>34</sup>

*Opioid-Naïve Prescribing.* We assessed whether each resident initiating transdermal fentanyl was opioid-naïve, defined as not having an opioid prescription with a duration end date within the two months prior to fentanyl initiation (e.g., the two-month window). Our definition of an opioid prescription included codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, and propoxyphene, as well as prescription drugs with these opioid active ingredients in combination with other analgesic ingredients, such as hydrocodone or oxycodone with acetaminophen (Figure 3.2).

*Persistent Pain.* We defined persistent pain as moderate-to-severe pain lasting 3 months or longer to follow the drug indication and other study approaches.<sup>2,16</sup> Each nursing home resident is assessed in the MDS at least every 3 months for the frequency and intensity of any pain over the previous 7 days.<sup>29</sup> This measurement has been found valid for measuring pain frequency and intensity in a scored scale.<sup>35</sup> We based our assessment of persistent pain on the most recent MDS pain measurements prior to transdermal fentanyl initiation. For our study, a nursing home resident was considered in persistent pain if the individual had two consecutive MDS reports, at least 90 days apart but no more than 180 days apart, with moderate or severe pain daily during the prior 7-day period.

*Covariates.* We evaluated whether certain individual and facility factors were associated with opioid-naïve status. For individual factors, we hypothesized that older age, poorer cognitive functioning, lower socioeconomic status (SES), and non-white race/ethnicity would be associated with greater opioid-naïve prescribing because these factors are related to worse care in nursing homes. We measured cognitive functioning in

the MDS measurement (at persistent pain onset) based on the CPS score from 0 (intact) to 4 (moderate-to-severe impairment). We measured SES based on highest completed education level and whether the resident paid for nursing home non-medical services out-of-pocket (“self-pay”). For facility factors, we hypothesized that smaller staff-to-resident ratio, fewer private pay residents, and for-profit status would be associated with greater opioid-naïve prescribing based on prior research on nursing home quality of care.<sup>25,36</sup> We obtained these facility measurements from the most recent OSCAR survey before fentanyl initiation.

We also identified potential confounders that could be associated with these individual and facility factors and opioid-naïve prescribing of transdermal fentanyl: gender, physical impairment, mood, family support, and facility compliance with federal law. We measured physical impairment in the most recent MDS (at or before fentanyl initiation) by the degree of assistance needed for activities of daily living (ADLs) under the Morris Additive Scale from 0 (no help required) to 28 (most help needed); mood at the most recent MDS (at or before fentanyl initiation) by the MDS Mood Scale score from 0 (no mood symptoms) to 8 (most mood symptoms); family support based on whether a family member or significant other participated in the most recent MDS care plan meeting (at or before fentanyl initiation); compliance with federal law based on whether there were any significant outstanding legal violations of federal nursing home requirements, as recorded in the most recent OSCAR survey at or before fentanyl initiation; and whether the resident had persistent pain under our definition.

### *Statistical Analysis*

We first assessed the proportion of residents in our study population receiving a transdermal fentanyl prescription who were (1) not in persistent pain or (2) opioid-naïve at fentanyl initiation. To test our hypothesis that certain individual and facility factors were associated with opioid-naïve prescribing, we fit a series of logistic regression models with opioid-naïve prescribing (versus not opioid-naïve prescribing) as the outcome.

The first models were univariate logistic regressions with one of the following predictors per model: age (categorized as <65 years, ≥65 to 74 years, ≥75 to 84 years, ≥85 years); race/ethnicity (White, Black, Hispanic, Asian, and other); cognitive functioning (categorized from 0-4 on the CPS Scale); self-pay status (yes versus no); education level (categorized as less than high school graduate, high school graduate, or college graduate/graduate school); facility staff hours per resident (categorized as <2.5 hours, ≥2.5 to 3.0 hours, ≥3.0 to 3.5-hours, ≥3.5 to 4 hours, ≥4.0 to 4.5 hours, ≥4.5 hours); facility proportion of self-pay residents (categorized as <10%, ≥ 10% to 30%, ≥ 30% to 50%, ≥ 50%); and facility for-profit status (yes versus no). We also conducted the univariate logistic regression for each confounder in our model: gender; degree of ADL assistance (categorized as 0, 1-7, 8-14, 15-21, 22-28 from the Morris Additive Scale), MDS Mood Scale (categorized as 0, 1-2, 3-4, 5-6, 7-8); family support (yes versus no); facility compliance with federal law (yes versus no); and persistent pain (yes versus no).

The next model included all of these variables in a multilevel logistic regression. Because residents are clustered within nursing homes and nursing homes are clustered

within states, we included random effects (i.e., intercepts) in all models for these two levels to ensure more accurate standard errors. Data were analyzed using SAS and Stata 13 software.

### *Sensitivity and Subgroup Analyses*

We conducted sensitivity analyses using a more stringent definition of opioid-naïve status (i.e., no opioid prescribing within a 6-month window prior to transdermal fentanyl initiation) and only residents with the highest fentanyl prescribing (dose $\geq$ 50 mcg/hour). We also restricted our study population to those residents whose last MDS assessment was within 10 days of fentanyl initiation, as well as those residents who did not have any temporary discharges (e.g., for hospitalizations) during the 2-month prior prescribing window. Because different diseases and health conditions can cause pain, we also conducted subgroup analysis in those residents with arthritis and diabetes, as recorded in the MDS.

## **RESULTS**

### *Persistent Pain*

Overall, only 8.2% of residents receiving transdermal fentanyl had persistent pain under our definition (i.e., at least 2 consecutive MDS assessments at least 90, but no more than 180, days apart with moderate or severe pain on a daily basis) (Table 3.1). Also, only 21.5% of residents had severe pain (i.e. moderate or severe pain on a daily basis) and 36.8% of residents had no pain at their last pain assessment before transdermal fentanyl initiation (Figure 3.3).

### *Opioid-Naïve Status*

A total of 36.3% of residents receiving transdermal fentanyl were opioid-naïve at initiation (Table 3.1). Of those residents with a prior opioid prescription, approximately 11% had a prescription for another long-acting drug (oxycodone hydrochloride or morphine sulfate extended release). Among all residents, a total of 57.1% were opioid-naïve at fentanyl initiation and did not have persistent pain, while only 6.6% had received an opioid prior to fentanyl initiation and were in persistent pain (Table 3.1).

### *Differences in Characteristics by Opioid-Naïve Status*

Residents who were or were not opioid-naïve differed by age, race, cognitive impairment, self-pay status, facility hours per resident, facility proportion of self-pay residents, facility for-profit status, physical impairment, family support, and persistent pain status (all  $p \leq 0.001$ ) (Table 3.2). There was no significant difference by gender ( $p=0.332$ ), resident education level ( $p=0.152$ ), facility average staff hours per resident ( $p=0.098$ ), resident mood ( $p=0.362$ ), or facility compliance with federal law ( $p=0.073$ ) (Table 3.2). Of those residents who were opioid-naïve, many also had prescriptions for antidepressants (54.4%), antipsychotics (21.8%), and mood stabilizing/anticonvulsant drugs (17.3%) (Table 3.3). Participants who were opioid-naïve, though, had lower percentages for antidepressant, antipsychotic, and anti-anxiety prescriptions compared to those who were not opioid-naïve (Table 3.3). Among opioid-naïve residents, approximately 20% were initiated at higher doses of transdermal fentanyl (50 mcg/hr or greater) (Table 3.3).

### *Multivariate Associations*

Opioid-naïve prescribing of transdermal fentanyl was associated with many individual resident factors (Table 3.4). In the multivariable logistic model, after accounting for mood, physical impairment, family support, and facility compliance with federal law, residents had a greater odds for opioid-naïve prescribing if they were older (compared to ages 65-74, ages 75-84 OR=1.16, 95% CI 1.04-1.29; ages 85-94 OR=1.30, 95% CI 1.16-1.44; ages >95 OR=1.69, 95% CI 1.46-1.95); more cognitively impaired (compared to intact cognitive functioning, borderline intact OR=1.06, 95% CI 0.93-1.20; mild impairment OR=1.31, 95% CI 1.16-1.47; moderate impairment OR=1.60, 95% CI 1.44-1.78; moderate-severe impairment OR=1.99, 95% CI 1.73-2.29); Asian (compared to White, OR=1.60, 95% CI 1.10-2.35); paid charges on their own (“self-pay” compared to non-self pay, OR=1.12, 95% CI 1.01-1.25); and increasing education (compared to education less than high school, high school graduate OR=1.09, 95% CI 1.01-1.17; college or graduate school OR=1.17, 95% CI 1.01-1.37). These associations for age, cognitive impairment, Asian race, and education were statistically significant (p-value≤0.05), except for borderline intact functioning (p-value=0.969).

The facility factors were not statistically significantly associated with opioid-naïve prescribing, except the facility’s average staff hours per resident in the 2.5-3.0 hour category and proportion of self-pay residents in the 10-30% and 30-50% categories had lower odds for opioid-naïve prescribing (compared to facilities with less than 2.5 average staff hours per resident, 2.5-3.0 hours OR=0.83, 95% CI 0.69-1.00; compared to facilities with less than 10% self-pay residents, ≥10% to 30% OR=0.85, 95% CI 0.77-0.95; ≥30 to 50% OR=0.86, 95% CI 0.75-0.98).



We also found associations with opioid-naïve status for other variables included in our model as controls for our hypothesis. Increasing number of ADLs requiring assistance was statistically significantly associated with increasing odds for opioid-naïve prescribing across the range of ADL assistance (for example, compared to 0 ADLs, 22-28 ADLs OR=1.47, 95% CI 1.20-1.81), while increasing MDS mood scale scores were statistically significantly associated with decreasing odds for opioid-naïve prescribing except for the highest category (for example, compared to 0 mood score, 5-6 mood score OR=0.82, 95% CI 0.71-0.96). Finally, persistent pain was statistically significantly associated with decreased odds for opioid-naïve prescribing (compared to no persistent pain, the persistent pain OR=0.44, 95% CI 0.38-0.51).

#### *Sensitivity and Subgroup Analyses*

The results from the sensitivity and subgroup analyses were consistent with these findings. For example, in the analysis including only residents with their last MDS assessment within 10 days prior to fentanyl initiation, we determined that 31.5% of these residents did not have any pain and 25.7% of the residents were opioid-naïve when they initiated prescription fentanyl. For all sensitivity and subgroup analyses, we found similar associations as our main analysis between resident factors and opioid-naïve initiation. Individual factors of increasing age, cognitive impairment, and number of ADLs requiring assistance were associated with increased odds for opioid-naïve fentanyl initiation, while increasing MDS mood scale scores and persistent pain were associated with decreased odds for opioid-naïve fentanyl initiation (Tables S3.A and S3.B). Many of these associations were statistically significant (Tables S3.A and S3.B).

## DISCUSSION

In our analysis of individual-level, nationally representative data capturing nursing home resident care, we found that over 90% of residents prescribed transdermal fentanyl did not have persistent pain and over one-third were opioid-naïve. These figures appear to indicate a significant failure to follow FDA warnings and practice guidelines for appropriate transdermal fentanyl initiation in nursing home residents. We also found that more vulnerable residents within nursing homes, particularly the oldest-old and most cognitively impaired, were more likely to initiate transdermal fentanyl inappropriately because they were opioid-naïve. These findings from a national nursing home population in 2008, after numerous FDA efforts to warn the public and health care practitioners about these transdermal fentanyl dangers, demonstrate the need for more effective risk communication and safer prescribing practices for long-acting opioids in nursing homes.

### *Persistent Pain*

We found that only 8.2% of residents in our study initiating transdermal fentanyl had persistent pain (i.e. moderate-to-severe daily pain on at least 2 consecutive MDS assessments at least 90, but no more than 180, days apart) (Table 3.1). Although this figure is higher than some persistent pain estimates for the general nursing home population,<sup>5</sup> this prevalence is extremely low for transdermal fentanyl initiators. This low persistent pain prevalence raises important concerns that transdermal fentanyl prescribing is not following FDA-approved labeling, which emphasizes that the drug should only be initiated in patients with moderate-to-severe continuous pain (i.e., persistent pain under our definition).<sup>15</sup> Our finding in the sensitivity analysis that at least

30% of residents did not have any pain within 10 days prior to initiating the transdermal fentanyl prescription reinforces this concern.

### *Opioid-Naïve Status*

We also found that 36.3% of the residents in our study initiating transdermal fentanyl did not receive any opioid prescription in the prior two-month window (i.e., opioid-naïve) (Table 3.1). This figure is similar to the results from another study, which found that 39.3% of 591 Medicaid residents in Rhode Island in 2004-2005 were opioid-naïve upon the initiation of a long-acting opioid. Our study results are concerning, because the FDA-approved labeling underscores that transdermal fentanyl should only be initiated in patients who are opioid-tolerant, so prescribing in opioid-naïve residents would clearly be inappropriate.<sup>15</sup> Furthermore, 20% of the opioid-naïve initiators in our study received the transdermal fentanyl prescription at higher doses ( $\geq 50$  mcg/hr), in contrast to precautions in the drug labeling and practice guidelines to initiate prescription opioids at the lowest doses and titrate upward if necessary (Table 3.3).<sup>9,10,15</sup>

### *Factors Associated with Opioid-Naïve Transdermal Fentanyl Initiation*

Our study of nursing home residents identified important factors independently associated with opioid-naïve initiation of transdermal fentanyl, including increasing age, greater cognitive impairment, and being Asian (Table 3.4). These effects remained even after adjustment for potential confounders: gender, number of ADL's requiring help, MDS mood score, presence of family support, facility compliance with federal law, and persistent pain. These effects increased steadily with increasing age and cognitive impairment, with the strongest effect for oldest age ( $\geq 95$  years with an OR=1.69) and greatest cognitive impairment (moderate-severe cognitive impairment with an OR=1.99).

These associations for increasing age, greater cognitive impairment, and non-white race are consistent with our hypothesis that residents with these factors would be more likely to initiate transdermal fentanyl without having a prior opioid prescription. The earlier study in Rhode Island nursing home residents also found a greater proportion of opioid-naïve initiators were older or had cognitive impairment compared to non-naïve initiators, although these effects were not statistically significant in a multivariate analysis.<sup>13</sup> Our study strengthens these findings and expands them to a national nursing home population.

The results raise important concerns about disparities in appropriate treatment for more vulnerable subpopulations within nursing homes. Prior studies, including our own, have found that approximately 15-25% of residents with non-cancer pain did not receive any analgesics.<sup>2,8,24</sup> These studies have also indicated that residents who are older, cognitively impaired, or non-White are less likely to receive prescription analgesics for non-cancer pain.<sup>8,24</sup> Thus, it is possible that prescription opioids are under-prescribed in some circumstances for residents with persistent pain but inappropriately prescribed for residents without such pain.

Our finding that residents with higher SES (self-pay status and more education) had greater odds for opioid-naïve initiation is counter to our hypothesis that higher SES would correspond with better care and more appropriate fentanyl prescribing (i.e., lower odds for opioid-naïve prescribing). Our findings may mean that residents with higher SES are more likely to receive transdermal fentanyl after experiencing any serious pain (whether persistent or acute) rather than first trying a short-acting opioid. This finding must be explored further.

We also did not find that the facility characteristics were associated with opioid-naïve initiation, in contrast to our hypothesis, except that the average hours per resident (in the 2.5-3.0 hours category) and the proportion of self-pay residents (in the 10-30% and 30-50% categories) were statistically significantly associated with lower odds for opioid-naïve prescribing. This finding for the self-pay categories is consistent with a prior study's conclusion that nursing home facilities with less than 10% private pay residents (and greater than 85% Medicaid residents) had poorer quality of care (measured by health deficiencies).<sup>37</sup> It is important to note for staff hours, though, that a recent systematic review cautioned against overreliance on staff numbers for the quality of care in nursing homes because of the importance of other staffing factors, such as staff turnover rates.<sup>36</sup>

Interestingly, although treated as a confounder in our model, an increase in a resident's number of ADLs requiring assistance was associated with higher odds (nearly 50% greater for the highest category) for opioid-naïve prescribing. Because we also included persistent pain as a factor in our multivariate model, any association between this pain status, physical impairment, and opioid-naïve prescribing (i.e., in a confounding relationship) would be controlled. In addition, an increase in a resident's mood indicators was associated with lower odds for opioid-naïve prescribing. This may indicate that residents with greater mood distress (e.g., verbal expression of distress, crying, tearfulness) are more likely to receive more appropriate pain medicine prescribing. One study found that residents with greater mood distress (on the MDS mood scale) were more likely to receive prescription analgesics for pain.<sup>24</sup>

## *Implications*

It appears from our study findings that policy makers and practitioners may need to consider further steps to ensure the appropriate use of transdermal fentanyl in nursing home residents. Our findings are more troubling given that FDA took additional actions to warn the public and practitioners on two occasions (2005 and 2007) about the dangers from initiating transdermal fentanyl in opioid-naïve patients and individuals without persistent pain, including serious injury or death.<sup>17-20</sup> Since our study's time period, FDA has implemented a Risk Evaluation and Mitigation Strategy (REMS) for long-acting opioids such as transdermal fentanyl that provides additional precautionary steps for their prescribing, such as healthcare provider training.<sup>38</sup> The REMS plan, though, does not include specific steps or information beyond the product labeling to ensure appropriate prescribing in the elderly, including nursing home residents. Concerns with opioid adverse events are generally even stronger in the elderly, particularly in vulnerable nursing home populations.<sup>9-11</sup>

Nursing home practices and policies could also require specific additional steps to ensure transdermal fentanyl is not prescribed to residents who do not have persistent pain and are opioid-naïve. In particular, our finding in the sensitivity analysis that over 30% of residents who initiated prescription fentanyl did not have any pain at their last assessment should be investigated further. Many recent efforts have focused on improving the quality of nursing home pain care and prescribing by multimodal approaches incorporating more accurate pain assessment methods, improved communication between staff and clinicians, options for pharmacological and non-pharmacological treatments, and education and training.<sup>39-41</sup> Polypharmacy in nursing

home residents is particularly harmful and challenging to address.<sup>42</sup> These efforts should also ensure that more vulnerable subpopulations within nursing homes (e.g., more cognitively impaired, older, and non-white residents) are not inappropriately prescribed transdermal fentanyl.

### *Strengths and Limitations*

Our study has important strengths. The source population included all nursing home residents in the United States in 2008 who received a transdermal fentanyl prescription, which strengthens the results' generalizability. In addition, we based our measures on comprehensive data for prescribing (Part D), resident traits (MDS), and facility characteristics (OSCAR). We were also able to examine individual and facility level factors, including SES, and control for potential confounders, including the residents' family support and facilities' compliance with federal law. Our conclusions are consistent with prior studies and expand on these earlier findings. Our study results were also similar in our sensitivity analyses using a less strict definition of opioid-naïve status (larger prior 6-month window) and including only those residents initiating transdermal fentanyl at the highest doses ( $\geq 50$  mg/hour). Both of these conditions (e.g., no opioid in prior 6 months and prescribing at highest fentanyl doses) raise even greater concerns for resident safety.

The study also has important limitations. First, for residents who had a prior opioid prescription at transdermal fentanyl initiation (and thus were not opioid-naïve), we did not also assess whether these residents were opioid-tolerant. The transdermal initiation for these residents would also be inappropriate under the FDA requirements if the prior opioid's total daily dose equivalent was not at least 25 mcg/hour transdermal

fentanyl.<sup>15</sup> However, the failure to prescribe any opioid prior to transdermal fentanyl initiation is the clearest and most significant deviation from these FDA requirements. From that perspective, our finding that more than one-third of nursing home residents were opioid-naïve at initiation is even more troubling.

Second, there was a time lag between the last MDS measurement and fentanyl initiation date for each resident, which averaged 33 days overall and was greater than 60 days for approximately 19% of the residents. This gap could mean that some residents developed persistent pain after the last MDS assessment that justified the fentanyl initiation. However, significant changes in resident pain status, such as the development of persistent pain requiring a long-acting opioid, would trigger an MDS assessment if considered a significant change in resident status.<sup>29</sup> To address any misclassification for persistent pain status, we restricted the sample in our sensitivity analysis to those residents with an MDS assessment no more than 10 days prior to fentanyl initiation and found similar results as our main analysis.

Third, our persistent pain definition may have misclassified some residents' fentanyl initiation as non-adherent to the drug labeling condition for pain when in fact they had continuous, moderate-to-severe pain that met this condition. In addition, if nursing home staff underestimated the intensity and/or duration for a resident's pain in the MDS, then our study would have incorrectly classified their fentanyl initiation as non-adherent to the persistent pain condition. However, our finding that 92% of residents did not have persistent pain is so high that misclassification seems unlikely to account for a sufficiently large amount to alleviate our adherence concerns. In addition, our sensitivity analysis showed that at least 30% of residents did not have any pain within 10 days prior



to initiating the transdermal fentanyl prescription. Even with the potential for MDS measurement error, this finding is still concerning.

Finally, the study's cross-sectional nature precludes examining any causal associations between factors and inappropriate fentanyl prescribing. However, we did obtain measurements for the individual factors prior to fentanyl prescribing, which helps address any concerns that the fentanyl prescribing could have affected these factors (such as the mood scale score).

## **CONCLUSION**

We have examined the critical public health issue of transdermal fentanyl prescribing in a large, vulnerable population and assessed whether the prescribing follows FDA requirements. Our findings, from a study population drawn from all nursing home residents in the United States, indicate that a large proportion of nursing home residents are receiving transdermal fentanyl inappropriately because they are not in persistent pain and are opioid-naïve. In addition, certain resident factors (i.e., being older, more cognitively impaired, and Asian) are associated with more frequent opioid-naïve prescribing. These results support the need for FDA, health care organizations, and nursing homes to continue their efforts to ensure appropriate transdermal fentanyl prescribing, with particular care for these more neglected subpopulations.

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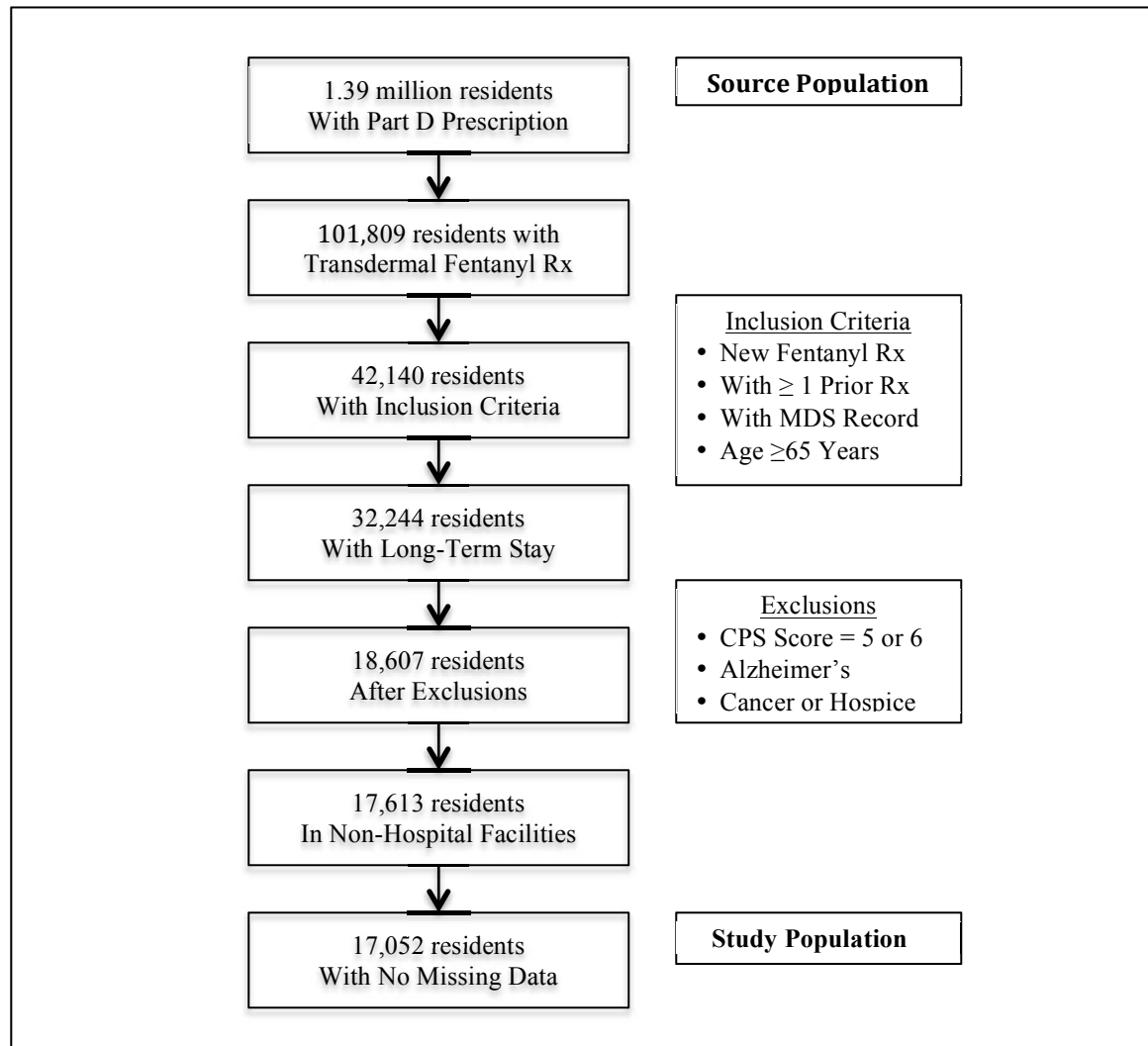
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## Figures and Tables

**Figure 3.1. Source and Study Populations from Part D and Minimum Data Set (2008).**

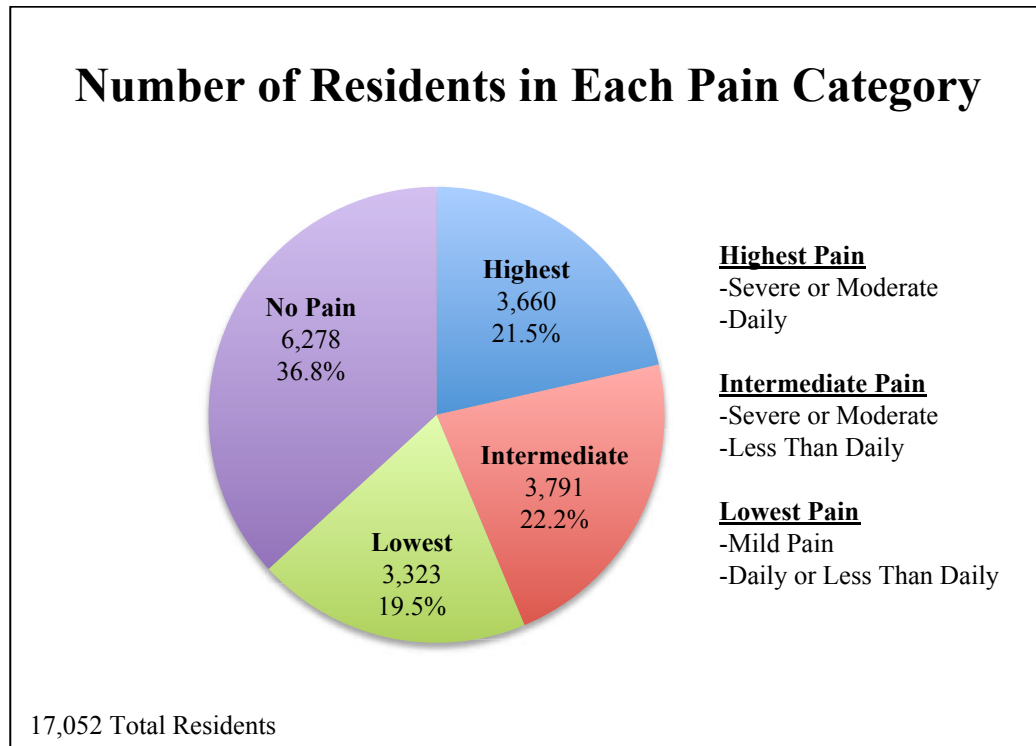


**Figure 3.2. Prescription Opioids.**

**Opioids (Mu Agonist)**

Codeine  
Fentanyl  
Hydrocodone  
Hydromorphone  
Levorphanol  
Meperidine  
Methadone  
Morphine  
Oxycodone  
Oxymorphone  
Propoxyphene

**Figure 3.3. Number of Residents in Different Pain Categories at Last Assessment Before Fentanyl ER Initiation.**





**Table 3.1. Numbers of Residents with Persistent Pain and Opioid-Naïve Initiation of Transdermal Fentanyl (n=17,052)\***

		<b>Opioid-Naïve Initiation</b>		
<b>Persistent Pain</b>		<b>No N (%)</b>	<b>Yes N (%)</b>	<b>Total Population</b>
	<b>No N (%)</b>	9,736 (57.1)	5,923 (34.7)	15,659 (91.8)
	<b>Yes N (%)</b>	1,126 (6.6)**	267 (1.6)	1,393 (8.2)
	<b>Total Population</b>	10,862 (63.7)	6,190 (36.3)	17,052 (100)

\* All percentages are based on total population of 17,052 residents in denominator.

\*\* Fentanyl prescribing complied with labeling conditions for persistent pain and no opioid-naïve initiation.

**Table 3.2. Fentanyl ER Prescribing: Characteristics of Nursing Home Residents Receiving New Fentanyl Extended Release Rx in 2008 by Opioid-Naïve Status (n=17,052)\***

	<b>Not Opioid-Naïve Initiation of Fentanyl ER N (%)**</b>	<b>Opioid-Naïve Initiation of Fentanyl ER N (%)**</b>	<b><u>X<sup>2</sup> Statistic</u> <u>p Value***</u></b>
<b>Total Population</b>	10,862 (63.7)	6,190 (36.3)	
<b>Characteristics</b>			
Gender			0.332
Female	8,574 (78.9)	4,847 (78.3)	
Male	2,288 (21.1)	1,343 (21.7)	
Age			<0.001
65-74	1,981 (18.2)	836 (13.5)	
75-84	3,771 (34.7)	1,979 (32.0)	
85-94	4,246 (39.1)	2,644 (42.7)	
≥95	864 (8.0)	731 (11.8)	
Race			<0.001
White	9,616 (88.5)	5,406 (87.3)	
Black	850 (7.8)	546 (8.8)	
Hispanic	274 (2.5)	154 (2.5)	
Asian	70 (0.6)	70 (1.1)	
Other	52 (0.5)	14 (0.2)	
Cognitive Impairment by CPS Score			<0.001
Intact=0	2,207 (20.3)	867 (14.0)	
Borderline	1,714 (15.8)	723 (11.7)	
Intact=1			
Mild	2,186 (20.1)	1,167 (18.9)	
Impairment=2			
Moderate	3,768 (34.7)	2,561 (41.4)	
Impairment=3			
Moderate-Severe	987 (9.1)	872 (14.1)	
Impairment=4			
Resident Self-Pay			<0.001
No	9,525 (87.7)	5,301 (85.6)	
Yes	1,337 (12.3)	889 (14.4)	
Education Level			0.152
< High School Graduate	4,340 (40.0)	2,406 (38.9)	
High School Graduate	5,923 (54.5)	3,406 (55.0)	
College Graduate	559 (5.5)	378 (6.1)	

Facility Average Staff Hours Per Resident			0.098
<2.5 Hours	508 (4.7)	305 (4.9)	
2.5-3.0 Hours	1,617 (14.9)	843 (13.6)	
3.0-3.5 Hours	3,174 (29.2)	1,903 (30.7)	
3.5-4.0 Hours	2,964 (27.3)	1,688 (27.3)	
4.0-4.5 Hours	1,594 (14.7)	912 (14.7)	
>4.5 Hours	1,005 (9.3)	539 (8.7)	
Facility's Proportion of Residents Self-Pay			0.001
<10%	1,649 (15.2)	1,030 (16.6)	
10-30%	6,408 (59.0)	3,502 (56.6)	
30-50%	2,299 (21.2)	1,314 (21.2)	
>50%	506 (4.7)	344 (5.6)	
Facility For Profit			0.040
No	3,449 (31.8)	2,060 (33.3)	
Yes	7,413 (68.3)	4,130 (66.7)	
ADL Help: Morris Additive Scale			<0.001
0 ADLs	467 (4.3)	167 (2.7)	
1-7 ADLs	1,365 (12.6)	558 (9.0)	
8-14 ADLs	1,976 (18.2)	990 (16.0)	
15-21 ADLs	4,333 (39.9)	2,537 (41.0)	
22-28 ADLs	2,721 (25.1)	1,938 (31.3)	
MDS Mood Scale			0.362
0	5,734 (52.8)	3,343 (54.0)	
1-2	2,712 (25.0)	1,543 (24.9)	
3-4	1,611 (14.8)	858 (13.9)	
5-6	690 (6.4)	376 (6.1)	
7-8	115 (1.1)	70 (1.1)	
Family Support			0.012
No	5,549 (51.1)	3,039 (49.1)	
Yes	5,313 (48.9)	3,151 (50.9)	
Facility Compliant with Federal Law			0.073
Yes	9,788 (90.1)	5,630 (91.0)	
No	1,074 (9.9)	560 (9.1)	
Persistent Pain			<0.001
No	9,736 (89.6)	5,923 (95.7)	
Yes	1,126 (10.4)	267 (4.3)	

Notes: Due to rounding, percentages do not all sum to 100. NSAID=Non-Steroidal Anti-Inflammatory Drug. ADL=Activities of Daily Living. CPS=Cognitive Performance Scale.

\* Excludes 561 (3.2%) observations with missing values.

\*\* All percentages correspond to column totals.

\*\*\* p value corresponds to the  $X^2$  statistic.

**Table 3.3. Additional Treatments or Medications for Nursing Home Residents in 2008 by Opioid-Naïve Status (n=17,052)\***

	<b>Not Opioid-Naïve Initiation of Fentanyl ER N (%)**</b>	<b>Opioid-Naïve Initiation of Fentanyl ER N (%)**</b>	<b>X<sup>2</sup> Statistic p Value***</b>
<b>Total Population</b>	10,862 (63.7)	6,190 (36.3)	
<b>Treatments</b>			
Muscle Relaxant			<0.001
No	9,969 (91.8)	5,949 (96.1)	
Yes	893 (8.2)	241 (3.9)	
Steroid			<0.001
No	9,539 (87.8)	5,679 (91.7)	
Yes	1,323 (12.2)	511 (8.3)	
Anti-Depressant			<0.001
No	3,547 (32.7)	2,804 (45.3)	
Yes	7,315 (67.3)	3,386 (54.7)	
Anti-Psychotic			0.657
No	8,481 (78.1)	4,815 (77.8)	
Yes	2,381 (21.9)	1,375 (22.2)	
Mood Stabilizing/Anti-Convulsant			<0.001
No	8,198 (75.5)	5,118 (82.7)	
Yes	2,664 (24.5)	1,072 (17.3)	
Anti-Anxiety			0.001
No	10,541 (97.0)	6,062 (97.9)	
Yes	321 (3.0)	128 (2.1)	
Physical Therapy			<0.001
No	8,704 (80.1)	4,802 (77.6)	
Yes	2,158 (19.9)	1,388 (22.4)	
Fentanyl ER Strength			<0.001
12.5 mcg/hr	2,688 (24.7)	1,629 (26.3)	
25 mcg/hr	6,280 (57.8)	3,330 (53.8)	
50 mcg/hr	1,469 (13.5)	847 (13.7)	
75 mcg/hr	247 (2.3)	235 (3.8)	
100 mcg/hr	178 (1.6)	149 (2.4)	

*Notes:* Due to rounding, percentages do not all sum to 100. NSAID=Non-Steroidal Anti-Inflammatory Drug. ADL=Activities of Daily Living. CPS=Cognitive Performance Scale.

\* Excludes 561 (3.2%) observations with missing values.

\*\* All percentages correspond to row totals.

\*\*\* p value corresponds to the X<sup>2</sup> statistic.

**Table 3.4. Odds Ratios for Noncompliant Prescribing of Fentanyl ER (No Opioid in Two Months Prior to New Fentanyl ER Prescription).**

	Univariate Models* (n=17,052)			Multivariate Model** (n=17,052)		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	1.05	0.97-1.14	0.231	1.08	0.99-1.18	0.069
Age						
65-74	(Ref)			(Ref)		
75-84	<b>1.24</b>	<b>1.12-1.38</b>	<b>&lt;0.001</b>	<b>1.16</b>	<b>1.04-1.29</b>	<b>0.007</b>
85-94	<b>1.47</b>	<b>1.32-1.62</b>	<b>&lt;0.001</b>	<b>1.30</b>	<b>1.16-1.44</b>	<b>&lt;0.001</b>
≥95	<b>1.99</b>	<b>1.73-2.28</b>	<b>&lt;0.001</b>	<b>1.69</b>	<b>1.46-1.95</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	<b>1.17</b>	<b>1.03-1.32</b>	<b>0.014</b>	1.09	0.96-1.24	0.173
Hispanic	1.01	0.81-1.26	0.914	0.94	0.75-1.17	0.566
Asian	<b>1.85</b>	<b>1.28-2.68</b>	<b>0.001</b>	<b>1.60</b>	<b>1.10-2.35</b>	<b>0.015</b>
Other	<b>0.52</b>	<b>0.28-0.97</b>	<b>0.039</b>	<b>0.50</b>	<b>0.27-0.94</b>	<b>0.033</b>
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.09	0.95-1.24	0.218	1.06	0.93-1.20	0.378
Intact=1						
Mild	<b>1.38</b>	<b>1.23-1.56</b>	<b>&lt;0.001</b>	<b>1.31</b>	<b>1.16-1.47</b>	<b>&lt;0.001</b>
Impairment=2						
Moderate	<b>1.83</b>	<b>1.65-2.04</b>	<b>&lt;0.001</b>	<b>1.60</b>	<b>1.44-1.78</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>2.40</b>	<b>2.09-2.76</b>	<b>&lt;0.001</b>	<b>1.99</b>	<b>1.73-2.29</b>	<b>&lt;0.001</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>1.17</b>	<b>1.06-1.29</b>	<b>0.002</b>	<b>1.12</b>	<b>1.01-1.25</b>	<b>0.031</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.02	0.95-1.10	0.543	<b>1.09</b>	<b>1.01-1.17</b>	<b>0.026</b>
Graduate						
College	1.12	0.97-1.30	0.120	<b>1.17</b>	<b>1.01-1.37</b>	<b>0.041</b>
Graduate						

Univariate Models (continued)				Multivariate Model (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.84	0.70-1.01	0.059	<b>0.83</b>	<b>0.69-1.00</b>	<b>0.048</b>
3.0-3.5 Hours	0.98	0.82-1.16	0.782	0.95	0.79-1.14	0.577
3.5-4.0 Hours	0.91	0.76-1.09	0.287	0.87	0.73-1.05	0.146
4.0-4.5 Hours	0.94	0.77-1.13	0.491	0.90	0.74-1.10	0.305
>4.5 Hours	0.90	0.73-1.10	0.299	0.86	0.69-1.06	0.157
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	<b>0.88</b>	<b>0.80-0.97</b>	<b>0.012</b>	<b>0.85</b>	<b>0.77-0.95</b>	<b>0.003</b>
30-50%	0.89	0.79-1.01	0.074	<b>0.86</b>	<b>0.75-0.98</b>	<b>0.022</b>
>50%	1.04	0.86-1.24	0.708	0.95	0.78-1.16	0.644
Facility For Profit						
No	(Ref)					
Yes	1.00	0.93-1.09	0.924	1.03	0.95-1.12	0.483
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.13	0.92-1.40	0.247	1.06	0.85-1.31	0.606
8-14 ADLs	<b>1.42</b>	<b>1.16-1.74</b>	<b>0.001</b>	<b>1.24</b>	<b>1.01-1.53</b>	<b>0.039</b>
15-21 ADLs	<b>1.68</b>	<b>1.38-2.04</b>	<b>&lt;0.001</b>	<b>1.35</b>	<b>1.11-1.65</b>	<b>0.003</b>
22-28 ADLs	<b>2.05</b>	<b>1.68-2.50</b>	<b>&lt;0.001</b>	<b>1.47</b>	<b>1.20-1.81</b>	<b>&lt;0.001</b>
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.97	0.90-1.05	0.481	<b>0.91</b>	<b>0.84-0.99</b>	<b>0.032</b>
3-4	0.93	0.84-1.03	0.163	<b>0.87</b>	<b>0.78-0.96</b>	<b>0.007</b>
5-6	0.93	0.80-1.07	0.302	<b>0.82</b>	<b>0.71-0.96</b>	<b>0.010</b>
7-8	1.05	0.76-1.45	0.774	0.85	0.62-1.19	0.348
Family Support						
No	(Ref)			(Ref)		
Yes	1.06	0.99-1.13	0.113	1.01	0.94-1.08	0.835
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.98	0.86-1.12	0.775	1.00	0.88-1.14	0.981
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>0.38</b>	<b>0.32-0.43</b>	<b>&lt;0.001</b>	<b>0.44</b>	<b>0.38-0.51</b>	<b>&lt;0.001</b>

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Univariate Logistic Models. This column presents the univariate logistic model results for each individual variable, unadjusted for the other variables.

\*\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; and resident persistent pain.

All regressions used multi-level modeling at the state and facility levels.

**Table S3.A. Sensitivity Analyses: Four Multi-Level Models.\* Odds Ratios for Noncompliant Prescribing of Fentanyl ER.**

	<b>Model 1: Keep Only Highest Fentanyl Strengths of 50, 75 and 100 mcg/hour (n=3,125)</b>			<b>Model 2: “Opioid-Naïve” Means No Opioid in 6 Months Prior to Fentanyl Initiation (n=16,260)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	1.02	0.86-1.23	0.797	<b>1.15</b>	<b>1.05-1.26</b>	<b>0.004</b>
Age						
65-74	(Ref)			(Ref)		
75-84	1.22	1.00-1.50	0.054	<b>1.30</b>	<b>1.15-1.47</b>	<b>&lt;0.001</b>
85-94	<b>1.26</b>	<b>1.01-1.57</b>	<b>0.037</b>	<b>1.58</b>	<b>1.39-1.78</b>	<b>&lt;0.001</b>
≥95	<b>1.85</b>	<b>1.26-2.72</b>	<b>0.002</b>	<b>2.12</b>	<b>1.81-2.49</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	1.10	0.84-1.44	0.486	1.14	0.98-1.31	0.080
Hispanic	1.01	0.62-1.63	0.983	0.95	0.74-1.21	0.673
Asian	0.64	0.22-1.84	0.406	<b>1.93</b>	<b>1.30-2.85</b>	<b>0.001</b>
Other	0.85	0.30-2.45	0.767	0.66	0.33-1.30	0.228
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.00	0.77-1.29	0.982	1.04	0.90-1.21	0.573
Intact=1						
Mild	1.20	0.94-1.52	0.143	<b>1.28</b>	<b>1.12-1.46</b>	<b>&lt;0.001</b>
Impairment=2						
Moderate	<b>1.30</b>	<b>1.04-1.63</b>	<b>0.021</b>	<b>1.79</b>	<b>1.59-2.02</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	1.31	0.95-1.79	0.098	<b>2.33</b>	<b>2.00-2.71</b>	<b>&lt;0.001</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	1.22	0.95-1.56	0.125	<b>1.24</b>	<b>1.10-1.38</b>	<b>&lt;0.001</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	0.95	0.80-1.12	0.513	<b>1.15</b>	<b>1.06-1.24</b>	<b>0.001</b>
Graduate						
College Graduate	<b>0.53</b>	<b>0.36-0.77</b>	<b>0.001</b>	<b>1.30</b>	<b>1.10-1.53</b>	<b>0.002</b>

Model 1 (continued)				Model 2 (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.93	0.64-1.36	0.723	<b>0.79</b>	<b>0.64-0.97</b>	<b>0.023</b>
3.0-3.5 Hours	0.93	0.65-1.32	0.677	0.88	0.72-1.07	0.196
3.5-4.0 Hours	1.08	0.75-1.55	0.687	0.84	0.69-1.02	0.079
4.0-4.5 Hours	1.06	0.72-1.57	0.763	0.85	0.69-1.05	0.137
>4.5 Hours	1.28	0.84-1.96	0.256	0.81	0.64-1.02	0.075
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	0.82	0.66-1.01	0.058	0.93	0.83-1.05	0.239
30-50%	0.84	0.63-1.10	0.201	0.93	0.81-1.08	0.335
>50%	0.95	0.61-1.49	0.828	1.05	0.85-1.29	0.679
Facility For Profit						
No	(Ref)			(Ref)		
Yes	1.04	0.86-1.26	0.708	1.00	0.91-1.09	0.953
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.36	0.82-2.26	0.233	1.08	0.85-1.37	0.541
8-14 ADLs	1.60	0.98-2.60	0.059	1.06	0.84-1.34	0.609
15-21 ADLs	<b>1.73</b>	<b>1.08-2.77</b>	<b>0.022</b>	1.21	0.97-1.51	0.096
22-28 ADLs	<b>2.08</b>	<b>1.27-3.37</b>	<b>0.003</b>	1.24	0.99-1.56	0.064
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	<b>0.87</b>	<b>0.72-1.05</b>	<b>0.140</b>	<b>0.89</b>	<b>0.81-0.97</b>	<b>0.008</b>
3-4	<b>0.92</b>	<b>0.74-1.16</b>	<b>0.505</b>	<b>0.77</b>	<b>0.69-0.87</b>	<b>0.000</b>
5-6	<b>0.79</b>	<b>0.55-1.12</b>	<b>0.184</b>	<b>0.80</b>	<b>0.68-0.93</b>	<b>0.005</b>
7-8	0.47	0.20-1.10	0.082	0.83	0.59-1.16	0.273
Family Support						
No	(Ref)			(Ref)		
Yes	<b>1.17</b>	<b>1.00-1.37</b>	<b>0.045</b>	1.01	0.94-1.09	0.809
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.95	0.71-1.26	0.700	1.05	0.91-1.21	0.489
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>0.65</b>	<b>0.50-0.84</b>	<b>0.001</b>	<b>0.44</b>	<b>0.37-0.52</b>	<b>&lt;0.001</b>



	<b>Model 3: Keep Only Residents with MDS Visit within 10 days prior to Fentanyl ER Rx (n=4,159)</b>			<b>Model 4: Keep Only Residents With No Discharge During Study Period (n=12,982)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	1.07	0.91-1.25	0.401	1.09	0.99-1.21	0.090
Age						
65-74	(Ref)			(Ref)		
75-84	1.00	0.82-1.22	0.997	<b>1.20</b>	<b>1.06-1.37</b>	<b>0.005</b>
85-94	1.19	0.97-1.45	0.089	<b>1.29</b>	<b>1.14-1.47</b>	<b>&lt;0.001</b>
≥95	<b>1.46</b>	<b>1.11-1.93</b>	<b>0.007</b>	<b>1.76</b>	<b>1.48-2.08</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
<b>Black</b>	<b>1.29</b>	<b>1.02-1.63</b>	<b>0.033</b>	1.06	0.91-1.25	0.118
Hispanic	1.09	0.73-1.64	0.665	0.97	0.74-1.27	0.657
Asian	1.16	0.61-2.19	0.656	<b>1.77</b>	<b>1.11-2.82</b>	<b>0.016</b>
Other	0.39	0.10-1.46	0.161	0.50	0.24-1.06	0.072
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.08	0.85-1.38	0.515	1.06	0.92-1.23	0.378
Intact=1						
Mild	1.22	0.97-1.54	0.082	<b>1.29</b>	<b>1.12-1.47</b>	<b>&lt;0.001</b>
Impairment=2						
Moderate	<b>1.62</b>	<b>1.31-1.99</b>	<b>&lt;0.001</b>	<b>1.57</b>	<b>1.39-1.78</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>1.92</b>	<b>1.47-2.51</b>	<b>&lt;0.001</b>	<b>2.06</b>	<b>1.75-2.43</b>	<b>&lt;0.001</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	0.95	0.76-1.17	0.609	<b>1.17</b>	<b>1.04-1.32</b>	<b>0.009</b>
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.08	0.94-1.25	0.265	<b>1.14</b>	<b>1.05-1.24</b>	<b>0.002</b>
Graduate						
College Graduate	0.99	0.72-1.36	0.953	<b>1.30</b>	<b>1.09-1.55</b>	<b>0.004</b>
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.92	0.65-1.30	0.641	<b>0.78</b>	<b>0.62-0.97</b>	<b>0.023</b>
3.0-3.5 Hours	0.95	0.68-1.32	0.748	0.93	0.76-1.15	0.514
3.5-4.0 Hours	0.90	0.64-1.26	0.534	0.86	0.70-1.07	0.171
4.0-4.5 Hours	0.99	0.69-1.42	0.963	0.85	0.68-1.07	0.174
>4.5 Hours	0.88	0.59-1.30	0.518	0.85	0.66-1.08	0.187

Model 3 (continued)				Model 4 (continued)		
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	<b>0.82</b>	<b>0.68-0.99</b>	<b>0.044</b>	<b>0.88</b>	<b>0.78-1.00</b>	<b>0.043</b>
30-50%	0.95	0.74-1.20	0.650	<b>0.86</b>	<b>0.74-1.00</b>	<b>0.049</b>
>50%	0.84	0.58-1.23	0.377	1.02	0.81-1.23	0.888
Facility For Profit						
No	(Ref)			(Ref)		
Yes	1.08	0.92-1.27	0.324	0.99	0.90-1.10	0.892
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.31	0.80-2.14	0.277	0.99	0.78-1.26	0.952
8-14 ADLs	1.35	0.85-2.16	0.207	1.16	0.93-1.46	0.191
15-21 ADLs	1.50	0.95-2.36	0.084	<b>1.25</b>	<b>1.01-1.56</b>	<b>0.043</b>
22-28 ADLs	1.53	0.96-2.43	0.075	<b>1.37</b>	<b>1.09-1.72</b>	<b>0.006</b>
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.89	0.75-1.05	0.178	0.93	0.84-1.02	0.127
3-4	0.89	0.72-1.10	0.274	<b>0.88</b>	<b>0.79-0.99</b>	<b>0.040</b>
5-6	<b>0.73</b>	<b>0.54-0.99</b>	<b>0.043</b>	<b>0.82</b>	<b>0.69-0.98</b>	<b>0.026</b>
7-8	0.74	0.38-1.41	0.356	0.85	0.59-1.22	0.376
Family Support						
No	(Ref)			(Ref)		
Yes	<b>1.16</b>	<b>1.01-1.32</b>	<b>0.032</b>	1.02	0.94-1.11	0.603
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	1.06	0.84-1.35	0.602	0.97	0.84-1.13	0.721
Persistent Pain						
No				(Ref)		
Yes	<b>0.42</b>	<b>0.31-0.56</b>	<b>&lt;0.001</b>	<b>0.44</b>	<b>0.37-0.52</b>	<b>&lt;0.001</b>

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; and resident persistent pain.

All regressions used multi-level modeling at the state and facility levels.

**Appendix S3.B. Subgroup Analysis by Disease or Condition: Two Multi-Level Models.\* Odds Ratios for Noncompliant Prescribing of Fentanyl ER.**

	<b>Model 1: Arthritis (n=7,310)</b>			<b>Model 2: Diabetes (n=6,015)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	1.06	0.92-1.23	0.437	1.01	0.88-1.16	0.889
Age						
65-74	(Ref)			(Ref)		
75-84	1.11	0.93-1.33	0.236	<b>1.19</b>	<b>1.02-1.39</b>	<b>0.024</b>
85-94	<b>1.26</b>	<b>1.05-1.50</b>	<b>0.011</b>	<b>1.29</b>	<b>1.09-1.52</b>	<b>0.003</b>
≥95	<b>1.67</b>	<b>1.33-2.09</b>	<b>&lt;0.001</b>	<b>2.03</b>	<b>1.51-2.73</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	0.98	0.80-1.22	0.877	1.05	0.88-1.27	0.573
Hispanic	0.76	0.51-1.15	0.194	1.09	0.80-1.49	0.570
Asian	1.64	0.85-3.16	0.139	1.71	0.97-3.01	0.062
Other	0.49	0.17-1.40	0.183	<b>0.37</b>	<b>0.13-1.03</b>	<b>0.058</b>
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.09	0.90-1.32	0.382	0.90	0.73-1.10	0.313
Intact=1						
Mild	<b>1.45</b>	<b>1.21-1.73</b>	<b>&lt;0.001</b>	<b>1.23</b>	<b>1.01-1.48</b>	<b>0.035</b>
Impairment=2						
Moderate	<b>1.49</b>	<b>1.26-1.76</b>	<b>&lt;0.001</b>	<b>1.45</b>	<b>1.22-1.73</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-	<b>2.00</b>	<b>1.59-2.50</b>	<b>&lt;0.001</b>	<b>1.59</b>	<b>1.25-2.01</b>	<b>&lt;0.001</b>
Severe						
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	1.14	0.97-1.34	0.118	0.95	0.77-1.17	0.622
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.06	0.94-1.18	0.338	1.11	0.99-1.26	0.080
Graduate						
College	1.17	0.91-1.50	0.233	1.15	0.88-1.52	0.307
Graduate						

Model 1: Arthritis (continued)				Model 2: Diabetes (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.88	0.66-1.17	0.381	0.88	0.64-1.20	0.406
3.0-3.5 Hours	0.89	0.67-1.17	0.402	1.03	0.76-1.38	0.859
3.5-4.0 Hours	0.83	0.62-1.09	0.184	0.98	0.72-1.33	0.895
4.0-4.5 Hours	0.84	0.62-1.14	0.258	1.02	0.74-1.41	0.890
>4.5 Hours	0.74	0.54-1.02	0.068	0.84	0.59-1.19	0.328
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	0.89	0.75-1.05	0.158	<b>0.81</b>	<b>0.69-0.95</b>	<b>0.008</b>
30-50%	0.95	0.78-1.16	0.601	<b>0.76</b>	<b>0.62-0.93</b>	<b>0.009</b>
>50%	0.95	0.71-1.28	0.760	0.93	0.66-1.32	0.685
Facility For Profit						
No	(Ref)					
Yes	1.06	0.94-1.21	0.352	1.00	0.87-1.15	0.985
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	0.91	0.65-1.29	0.597	1.32	0.86-2.03	0.197
8-14 ADLs	1.22	0.88-1.69	0.240	1.50	1.00-2.26	0.052
15-21 ADLs	<b>1.41</b>	<b>1.03-1.94</b>	<b>0.032</b>	<b>1.82</b>	<b>1.23-2.71</b>	<b>0.003</b>
22-28 ADLs	<b>1.51</b>	<b>1.09-2.10</b>	<b>0.013</b>	<b>1.97</b>	<b>1.31-2.95</b>	<b>0.001</b>
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.97	0.86-1.10	0.653	1.00	0.87-1.16	0.952
3-4	<b>0.82</b>	<b>0.70-0.96</b>	<b>0.012</b>	0.90	0.75-1.08	0.254
5-6	0.85	0.69-1.05	0.140	1.01	0.79-1.29	0.959
7-8	0.84	0.53-1.35	0.478	0.94	0.53-1.67	0.842
Family Support						
No	(Ref)			(Ref)		
Yes	1.03	0.93-1.15	0.550	1.07	0.95-1.20	0.254
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.94	0.77-1.13	0.500	1.12	0.91-1.37	0.273
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>0.44</b>	<b>0.35-0.55</b>	<b>&lt;0.001</b>	<b>0.53</b>	<b>0.42-0.67</b>	<b>&lt;0.001</b>

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; and resident persistent pain.

All regressions used multi-level modeling at the state and facility levels.

**CHAPTER 4: INAPPROPRIATE CO-PRESCRIBING WITH  
LONG-ACTING OXYCODONE AMONG NURSING HOME  
RESIDENTS IN THE UNITED STATES**

## **Abstract**

Objective: Due to its risks, FDA approved extended-release oxycodone hydrochloride (oxycodone ER) only for use in individuals with moderate-to-severe, continuous pain. FDA also cautioned against individuals taking other central nervous system (CNS) depressants simultaneously with oxycodone ER. Our objective was to quantify the prevalence of oxycodone ER prescribing in elderly nursing home residents without moderate-to-severe, continuous pain and with any CNS depressant co-prescribing, as well as the association of individual and facility traits with this co-prescribing.

Design: Cross-sectional study.

Setting: Linked Minimum Data Set (MDS) assessments; Online Survey, Certification and Reporting (OSCAR) records; and Medicare Part D claims.

Participants: From a cross-section of all long-stay U.S. nursing home residents in 2008 with an MDS assessment and Medicare Part D enrollment, we identified individuals ( $\geq 65$  years old) who initiated oxycodone ER, excluding those with Alzheimer's, severe cognitive impairment, cancer or receipt of hospice care.

Measurements: We used Medicare Part D to select beneficiaries initiating oxycodone ER between December 1, 2007, and November 30, 2008, and examined whether they had persistent pain or were co-prescribed any CNS depressant within the 30 days (the "window") after the first oxycodone ER prescription. A CNS drug was co-prescribed if

any day within the prescription's duration (prescription date to the end of days supply) overlapped with the 30-day window. A CNS depressant included a sedative, hypnotic, atypical antipsychotic, antiemetic, or muscle relaxant. We obtained resident and facility characteristics from MDS and OSCAR records and defined persistent pain as moderate-to-severe, daily pain on consecutive MDS assessments at least 90 days, but no more than 180 days, apart. We estimated associations of patient and facility attributes and CNS depressant co-prescribing at oxycodone ER initiation using multilevel mixed effects logistic regression analyses.

Results: Among 4,317 residents who initiated oxycodone ER, 1,147 (26.6%) were co-prescribed a CNS depressant and 3,801 (88.1%) did not have persistent pain. Nearly 4% of residents were co-prescribed 2 or more CNS depressants. In the regression analysis with adjustments, residents who were older (compared to ages 65-75, ages 75-84 odds ratio (OR)=0.77, 95% CI=0.64-0.92; ages 85-94 OR=0.52, 95% CI 0.43-0.64; ages  $\geq 95$  OR= 0.38, 95% CI = 0.24-0.60); Black (compared to White, OR=0.60, 95% CI=0.44-0.81) or more cognitively impaired (compared to no cognitive impairment, mild impairment OR=0.71, 95% CI=0.57-0.88; moderate impairment OR=0.52, 95% CI=0.42-0.65; moderate-severe cognitive impairment, OR=0.32, 95% CI = 0.21-0.49) were less likely to have CNS depressant co-prescribing.

Conclusion: Most nursing home residents initiating oxycodone ER did not have persistent pain and many were co-prescribed a CNS depressant. Changes in prescribing practices may be necessary to ensure FDA warnings are followed.

## INTRODUCTION

More than 1.4 million Americans reside in nursing homes, where they receive critical medical and daily care.<sup>1</sup> This population will increase as the elderly population grows in the United States.<sup>2</sup> Elderly nursing home residents suffer from numerous diseases, poorer health, and greater frailty than the general population, which can lead to significant cognitive and physical decline.<sup>2</sup> Many residents also experience debilitating pain from these health conditions.<sup>3</sup> Nursing homes face many challenges in effectively identifying and treating residents' adverse health conditions, including their pain.<sup>2</sup>

Nursing homes frequently rely on pharmaceutical therapies for disease treatment and pain management. This approach can be effective for many conditions and types of pain if nursing home practitioners carefully select, administer and monitor the prescription drug use.<sup>4-6</sup> However, inappropriate drug prescribing can threaten patient safety because of potential adverse effects. One study estimated that over 50 percent of elderly nursing home residents receive at least one potentially inappropriate prescription each year.<sup>7</sup> The elderly are more susceptible to drug adverse events because of their pharmacokinetic and pharmacodynamic differences from the general population and diminished resilience.<sup>4-6</sup>

Nursing home residents are particularly vulnerable to the harms from inappropriate prescribing because they use more medications and have more co-morbid conditions.<sup>8-10</sup> The prescribing of multiple drugs together can also cause interactive effects in a patient.<sup>11</sup> This co-prescribing of numerous drugs to an individual ("polypharmacy") has been identified as a serious risk factor for adverse events in



nursing homes.<sup>8,12</sup> One study in the elderly found that 26% of patients with osteoarthritis were inappropriately prescribed an opioid because of potential drug-drug interactions.<sup>11</sup>

The U.S. Food and Drug Administration (FDA) plays an important role in ensuring appropriate pharmaceutical use by evaluating each prescription drug's safety and efficacy before approval. The indications for each drug's use, approved by FDA, are included in the drug labeling.<sup>13</sup> The labeling also includes any warnings and cautions about possible side effects, including safety risks to specific types of patients and potential dangerous interactions with other drugs.<sup>13</sup> The Centers for Medicare and Medicaid Services (CMS), which establishes federal standards for all nursing homes receiving Medicare and/or Medicaid funds, including proper medication use, recommends nursing homes follow FDA labeling conditions for drug prescribing.<sup>14</sup>

FDA's role in ensuring prescription drug safety has been particularly visible in the agency's regulation of opioids. Opioids are prescribed frequently in nursing homes to treat residents' pain but also present important safety risks.<sup>3,15</sup> FDA approved extended release (ER) formulations for opioids that provide a longer drug release in the patient's body.<sup>16</sup> Oxycodone hydrochloride ("oxycodone") ER, available since the 1990's, is a widely used opioid in nursing homes.<sup>3,17</sup> Oxycodone ER, like other opioids, affects the body's central nervous system (CNS).<sup>18,19</sup> Although effective in treating more serious pain over a longer duration, the drug can increase a patient's risk for severe respiratory depression upon first being administered.<sup>18,19</sup> The FDA-approved labeling warns of this risk and emphasizes that the drug is only for patients with moderate-to-severe, continuous pain.<sup>18</sup>

The drug labeling also cautions against use of oxycodone ER in combination with other CNS depressants, specifically phenothiazines (typical psychotics), sedatives, hypnotics, and antiemetics, as well as muscle relaxants.<sup>18</sup> The use of these CNS depressants in combination with oxycodone ER presents serious risks for respiratory depression in patients, which can be fatal, as well as profound sedation or coma.<sup>18,19</sup> The labeling also warns that the elderly are even more susceptible to these side effects.<sup>18</sup>

The risks from concomitant drug use with opioids are not limited to CNS depressants. The co-prescribing of other CNS drugs, such as atypical antipsychotics and antidepressants, with opioids increases the risks for psychoactive adverse events, including delusions and sedation.<sup>20</sup> The CMS nursing home guidelines recommend more broadly against the co-administration of CNS drugs (not just CNS depressants) because of this potential for adverse drug interactions.<sup>14,21</sup>

To determine whether oxycodone ER prescribing in this vulnerable elderly population has complied with the indications approved by FDA, we assessed data on nursing home residents, facilities, and medication prescribing in 2008 from the national Minimum Data Set (MDS), the Online Survey, Certification, and Reporting (OSCAR) database, and Medicare Part D. Specifically, we evaluated the extent of this oxycodone ER prescribing for elderly nursing home residents and determined whether residents receiving these opioid prescriptions for the first time had moderate-to-severe, continuous pain (referred to as “persistent pain”) and were co-prescribed any CNS depressant listed in the FDA warning. We then assessed whether certain individual and facility-level factors were associated with co-prescribing of a CNS depressant. Finally, based on the broader CMS recommendation against co-prescribing of CNS drugs, including opioids,

we assessed oxycodone ER co-prescribing with more comprehensive CNS drug categories and any associated factors.

## METHODS

### *Participants*

Our study's source population was the approximately 1.4 million individuals who resided in a nursing home in the United States at any time between December 1, 2007, and November 30, 2008, and had at least one prescription drug documented in a Part D record. Approximately 81% of nursing home residents were estimated to have enrolled in the Part D program in 2006 just prior to our study period.<sup>22</sup> The Part D prescription record provides information about the drug, dose, dosage form strength, and days supply.<sup>23</sup> We also relied on MDS measurements to create our study population. All United States nursing homes are required by federal law (for Medicare and/or Medicaid certification) to use the MDS survey instrument to assess each nursing home resident periodically.<sup>2</sup>

*Inclusion Criteria.* Only those residents who received an oxycodone ER prescription between December 1, 2007, and November 30, 2008, were eligible for the study population, with 29,489 residents (2.0% of the source population) (Figure 4.1). We then only included residents with at least one MDS record before initiating the oxycodone ER drug. We defined this initiation as the date of a resident's first prescription for oxycodone ER during the December 1, 2007 to November 30, 2008 time period. We also defined the "duration end date" for each prescription by adding the number of days' supply to the prescription date. Only new oxycodone ER users were included in the study population, defined as those residents who did not have an earlier

oxycodone ER prescription (or prescription duration end date) within two months prior to initiation. In addition, only those residents who had at least one Part D prescription during this 2-month prior window, as well as during the one-month period after initiation, and who were 65 years or older were eligible for our study. Finally, we only included those residents who had a long-term stay (defined as at least 90 continuous days) prior to their study drug initiation. There were 6,348 eligible residents who met these criteria (Figure 4.1).

*Exclusion Criteria.* We excluded those individuals who had cancer or were terminally ill because of the distinct pain management issues faced by this patient population. We also excluded those with Alzheimer's disease or most severe cognitive impairment, defined as an MDS Cognitive Performance Scale (CPS) score of 5 or 6 (Figure 4.1), because of the difficulty in assessing accurately their pain levels,<sup>24</sup> which could affect analgesic prescribing. After these exclusions, 4,606 individuals with oxycodone ER remained in our study population. After excluding those who resided in hospital-based facilities, we dropped 112 (2.5%) residents who were missing data for at least one covariate in our analysis. Our final study population consisted of 4,317 residents with oxycodone ER (Figure 4.1).

### *Measures*

We analyzed data from the MDS about each nursing home resident initiating oxycodone ER. The MDS is a standardized survey instrument measuring each resident on fifteen domains, including any degree of pain, cognitive and physical functioning, psychosocial well-being, activities and diseases.<sup>25</sup> The MDS assessor, a trained nursing home staff person, relies on personal observation, interviews with residents, resident

medical records, discussions with resident family, and consultation with clinicians and other staff to complete the MDS questions and record all information on the MDS forms.<sup>25,26</sup> The information gathered for the MDS is then used by the nursing home to develop individual care plans for each resident.<sup>2,26</sup> The nursing home assesses each resident every three months for certain MDS measures (including cognitive and physical functioning, mood, and pain) and annually for all MDS measures and when any significant change in resident status occurs.<sup>25</sup>

Our study relied on the MDS 2.0 version, which was used during our 2007-08 study period. The MDS 2.0 measures in our study have been found generally reliable and valid for the domains when used by trained staff.<sup>27</sup> For example, MDS 2.0 items have been incorporated into other valid and reliable instruments (e.g., MDS ADL Scale, MDS Cognitive Performance Scale) to measure resident characteristics, such as physical and cognitive functioning.<sup>27-29</sup> We also relied on OSCAR data for measurement of facility factors, such as the facility's staff-to-resident ratio, percentage of private pay residents, for-profit status, and compliance with federal law. The federal government compiles annually in OSCAR this information about each nursing home facility.<sup>30</sup>

*Co-Prescribing of Central Nervous System (CNS) Depressants and Agents.* We assessed whether each resident initiating oxycodone ER was co-prescribed a CNS depressant, defined as having at least one CNS depressant prescription (or prescription duration end date) within a 30-day period after study drug initiation (e.g., the one-month window). This approach is consistent with the method used in other studies.<sup>11</sup> Our definition of a CNS depressant followed the FDA warning and included any sedative, hypnotic, atypical antipsychotic, muscle relaxant, or antiemetic drug (Figure 4.2a). We

also assessed alternatively whether each resident was co-prescribed a CNS agent, defined more broadly as any antidepressant, antipsychotic (typical and atypical), anti-anxiety, mood stabilizer, or muscle relaxant drug (Figure 4.2b).

*Persistent Pain.* We defined persistent pain as moderate-to-severe pain lasting 3 months or longer, which follows the drug indication and other study approaches.<sup>3,31</sup> Each nursing home resident is assessed in the MDS at least every 3 months for the frequency and intensity of any pain over the previous 7 days.<sup>25</sup> This measurement has been found valid for measuring pain frequency and intensity in a scored scale.<sup>32</sup> We based our assessment of persistent pain on the most recent MDS pain measurements prior to study drug initiation. For our study, a nursing home resident was considered in persistent pain if the individual had two consecutive MDS reports, at least 90 days apart but no more than 180 days apart, with moderate or severe pain daily during the prior 7-day period.

*Covariates.* We evaluated whether certain individual and facility factors were associated with CNS depressant co-prescribing. For individual factors, we hypothesized that older age, poorer cognitive functioning, lower socioeconomic status (SES), and non-white race/ethnicity would be associated with greater CNS depressant co-prescribing because these factors are related to worse care in nursing homes.<sup>15,24,33</sup> We measured cognitive functioning in the MDS measurement (at persistent pain onset) based on the CPS score from 0 (intact) to 4 (moderate-to-severe impairment). We measured SES based on highest completed education level and whether the resident paid for nursing home non-medical services out-of-pocket (“self-pay”). For facility factors, we hypothesized that smaller staff-to-resident ratio, fewer private pay residents, and for-profit status would be associated with greater CNS depressant co-prescribing based on

prior research on nursing home quality of care.<sup>34,35</sup> We obtained these facility measurements from the most recent OSCAR survey before oxycodone ER initiation.

We also identified potential confounders that could be associated with these individual and facility factors and CNS co-prescribing with the study drug: gender, physical impairment, mood, family support, facility compliance with federal law, and mental health condition. We measured physical impairment in the most recent MDS (at or before study drug initiation) by the degree of assistance needed for activities of daily living (ADLs) under the Morris Additive Scale from 0 (no help required) to 28 (most help needed); mood at the most recent MDS (at or before fentanyl initiation) by the MDS Mood Scale score from 0 (no mood symptoms) to 8 (most mood symptoms); family support based on whether a family member or significant other participated in the most recent MDS care plan meeting (at or before study drug initiation); compliance with federal law based on whether there were any significant outstanding legal violations of federal nursing home requirements, as recorded in the most recent OSCAR survey at or before study drug initiation; and mental health condition based on whether the MDS recorded at least one of the following diagnoses: depression, anxiety disorder, bi-polar disorder, or schizophrenia.

### *Statistical Analysis*

We first assessed the proportion of residents in our study populations receiving an oxycodone ER prescription, who were (1) not in persistent pain or (2) co-prescribed a CNS depressant. We also assessed the proportion of residents who were co-prescribed a CNS agent. To test our hypothesis that certain individual and facility factors were associated with CNS depressant co-prescribing, we fit a series of logistic regression

models with CNS depressant co-prescribing (versus no CNS depressant co-prescribing) as the outcome.

The first models were univariate logistic regressions with one of the following predictors per model: age (categorized as 65-74 years, 75 to 84 years, 85 to 94 years,  $\geq 95$  years); race/ethnicity (White, Black, Hispanic, and other); cognitive functioning (categorized from 0-4 on the CPS Scale); self-pay status (yes versus no); education level (categorized as less than high school graduate, high school graduate, or college graduate/graduate school); facility staff hours per resident (categorized as  $<2.5$  hours,  $\geq 2.5$  to 3.0 hours,  $\geq 3.0$  to 3.5-hours,  $\geq 3.5$  to 4 hours,  $\geq 4.0$  to 4.5 hours,  $\geq 4.5$  hours); facility proportion of self-pay residents (categorized as  $<10\%$ ,  $\geq 10\%$  to 30%,  $\geq 30\%$  to 50%,  $\geq 50\%$ ); and facility for-profit status (yes versus no). We also conducted the univariate logistic regression for each confounder in our model: gender; degree of ADL assistance (categorized as 0, 1-7, 8-14, 15-21, 22-28 from the Morris Additive Scale), MDS Mood Scale (categorized as 0, 1-2, 3-4, 5-6, 7-8); family support (yes versus no); facility compliance with federal law (yes versus no); the existence of at least one mental health condition (yes versus no); and persistent pain (yes versus no).

The next model included all of these variables in a multivariable logistic regression. Because residents are clustered within nursing homes and nursing homes are clustered within states, we included random effects (i.e., intercepts) in all models for these two levels to ensure more accurate standard errors. In addition, we conducted sensitivity analyses using a more stringent definition of CNS depressant co-prescribing (i.e., at least 2 CNS depressants) and restricted our study population to those residents whose last MDS assessment was within 30 days of oxycodone ER initiation. For



comparison, we also conducted additional multivariable logistic regression analyses with CNS agent co-prescribing as an alternative outcome (i.e., co-prescribing with at least 2 CNS agents in the first model and at least 3 CNS agents in the second model). Data were analyzed using SAS and Stata 13 software.

## **RESULTS**

### *Persistent Pain*

Only 12.0% of residents receiving oxycodone ER had persistent pain under our definition (i.e., at least 2 consecutive MDS assessments at least 90, but no more than 180, days apart with moderate or severe pain on a daily basis) (Table 4.1). In addition, only 29.3% of residents with oxycodone ER had severe pain (i.e. moderate or severe pain on a daily basis) and only 28.5% of residents had no pain at their last pain assessment before oxycodone ER initiation (Figure 4.3).

### *Co-Prescribing Status*

A total of 27% of residents initiating oxycodone ER were co-prescribed a drug in at least one CNS depressant category (Table 4.1). Among all residents initiating oxycodone ER, approximately 8% had persistent pain and were not co-prescribed any CNS depressants (Table 4.1). In addition, approximately 4% of residents initiating oxycodone ER were co-prescribed drugs in at least two CNS depressant categories, although few residents were co-prescribed drugs in more than two CNS depressant categories (Table 4.2). Only 6% of residents initiated oxycodone ER at higher doses (>20 mg), although this figure was slightly higher (8%) for those with CNS depressant co-prescribing (Table 4.3).

The most commonly co-prescribed CNS depressants were hypnotics (11%); muscle relaxants (9%); and antiemetics (8%) (Table 4.4). Sedatives were only prescribed for 3% of residents, with no barbiturates and very few benzodiazepines ( $\leq 1\%$ ) (Table 4.4). Typical psychotics were rarely prescribed ( $\leq 1\%$ ) (Table 4.4). Most CNS depressants were co-prescribed in only one category, but the most frequent co-prescribing combinations were the hypnotic-antiemetic, hypnotic-muscle relaxant, and antiemetic-muscle relaxant categories (Table 4.5).

In our alternate analysis, 38% of residents initiating oxycodone ER were co-prescribed drugs in at least two CNS agent categories; 10% in at least three CNS agent categories; and 1% in at least four CNS agent categories (Table 4.6). Only 6% of residents with CNS agent co-prescribing received oxycodone ER prescriptions at higher doses ( $>20$  mg) (Table 4.7). The most commonly prescribed CNS agents were antidepressants (72%); mood stabilizers (29%) and antipsychotics (20%) (Table 4.8). Atypical psychotic drugs were over 98% of the co-prescribed drugs in the antipsychotic category. Only 3% of oxycodone ER initiators were prescribed any anti-anxiety drug, primarily buspirone (Table 4.8). The most frequently prescribed two-category combinations were antidepressants-mood stabilizers (14%) and antidepressants-antipsychotics (9%) (Table 4.9). The most frequently prescribed three-category combination was antidepressants-antipsychotics-mood stabilizers (5%) (Table 4.9). We also found that nearly 80% of antipsychotic prescribing was for off-label uses (no diagnosed bipolar disorder or schizophrenia) (Table 4.10).

The residents in our study population received prescriptions for 12 different drugs on average (based on the median value) within the 30-day window. Our analysis found

that 80% of oxycodone ER initiators were prescribed 9 or more total drugs, a common threshold for identifying polypharmacy (Table 4.11). Approximately 3% of residents had prescriptions for 29 or more drugs during the one-month window after oxycodone ER initiation (Table 4.11).

#### *Differences in Characteristics By Co-Prescribing Status*

Oxycodone ER initiators who were or were not co-prescribed a CNS depressant differed by age, cognitive impairment, resident self-pay status, facility proportion of residents with self-pay status, facility for-profit status, family support, persistent pain status, and mental health condition (all  $p \leq 0.001$ ) (Table 4.12). There was no significant difference in CNS depressant co-prescribing status by gender ( $p=0.496$ ), race ( $p=0.051$ ), education level ( $p=0.467$ ), facility average staff hours per resident ( $p=0.490$ ), MDS mood scale ( $p=0.592$ ), or facility compliance with federal law ( $p=0.566$ ). (Table 4.12).

#### *Multivariate Associations*

CNS depressant co-prescribing with oxycodone ER was associated with many individual resident factors (Table 4.13). In the multivariable logistic model, after accounting for mood, physical impairment, family support, facility compliance with federal law, persistent pain status, and mental health condition, residents had a *lower* odds for CNS depressant co-prescribing if they were older (compared to ages 65-74, ages 75-84 OR=0.77, 95% CI 0.64-0.92; ages 85-94 OR=0.52, 95% CI 0.43-0.64; ages >95 OR=0.38, 95% CI 0.24-0.60); Black (compared to Whites, OR=0.60, 95% CI 0.44-0.81); and more cognitively impaired (compared to intact cognitive functioning, borderline intact OR=0.89, 95% CI 0.73-1.10; mild impairment OR=0.71, 95% CI 0.57-0.88; moderate impairment OR=0.52, 95% CI 0.42-0.65; moderate-severe impairment

OR=0.32, 95% CI 0.21-0.49). These associations for age, Black race, and cognitive impairment were statistically significant ( $p \leq 0.001$ ), except for borderline intact functioning ( $p$ -value=0.289). The facility factors in our hypothesis were not statistically significantly associated with CNS depressant co-prescribing for either morphine or oxycodone ER initiators.

#### *Sensitivity Analyses*

The results from our two sensitivity analyses were consistent with these findings, because the factors of older age, increasing cognitive impairment and Black race had *lower* odds for CNS depressant co-prescribing in both models (Appendix S4.A). These effect estimates were more pronounced in the model assessing odds for CNS depressant co-prescribing in at least two categories (for example, age  $\geq 95$  OR=0.08, 95% CI 0.01-0.59 and moderate-severe cognitive impairment OR=0.19, 95% CI 0.04-0.83) (Appendix S4.A). In this same sensitivity model, male gender also had *lower* odds for co-prescribing (OR=0.48, 95% CI 0.30-0.77).

#### *Alternate Analyses*

In our alternate analyses (i.e., using broader CNS agent categories), the factors of male gender, older age, and resident self-pay status were statistically significantly associated with *lower* odds for CNS agent co-prescribing in 2 categories (for example, male OR=0.82, 95% CI 0.70-0.96; age  $\geq 95$  OR= 0.22, 95% CI 0.15-0.33; self-pay status OR=0.80, 95% CI 0.65-0.99), while increasing cognitive impairment was statistically significantly associated with *higher* odds for CNS agent co-prescribing in 2 categories (for example, moderate-severe impairment OR=1.70, 95% CI 1.22-2.35) (Appendix S4.B). Residents with increasing MDS Mood scale score also had *higher* odds for co-

prescribing in 2 CNS agent categories (for example, MDS mood score 7-8 OR=2.60, 95% CI 1.25-5.43) (Appendix S4.B). This association was even stronger for the outcome with co-prescribing in 3 CNS agent categories (MDS mood score 7-8 OR=3.70, 95% CI 1.63-8.39).

## DISCUSSION

In our analysis of individual-level, nationally representative data capturing nursing home resident care, we found that nearly 90% of residents prescribed transdermal fentanyl did not have persistent pain and over one-quarter were co-prescribed a CNS depressant. These figures appear to indicate a significant failure to follow FDA warnings for appropriate oxycodone ER use in nursing home residents. Even if CNS depressant co-prescribing was medically justified for some residents, our finding that nearly 40% of oxycodone ER users were co-prescribed 2 or more other CNS agents raises important safety concerns from potential drug interactions. These findings from a national nursing home population in 2008, after FDA and CMS efforts to warn the public and health care practitioners about co-prescribing dangers, demonstrate the need for more effective risk communication and safer prescribing practices for long-acting opioids in nursing homes.

### *Persistent Pain*

Overall, we found that only 12.0% of residents receiving oxycodone ER had persistent pain under our definition (Table 4.1). In addition, only 29.3% of residents had severe pain (i.e. moderate or severe pain on a daily basis) at their last pain assessment before oxycodone ER initiation (Figure 4.3). Most surprisingly, 28.5% had no pain at their last assessment before initiation (Figure 4.3). Even for those residents with an MDS assessment 5 days or less before drug initiation, over 20% had no pain. These findings

indicate that oxycodone ER prescribing for many residents did not follow the FDA's approved labeling condition that the drug only be used for moderate-to-severe, continuous pain.

#### *Co-Prescribing of CNS Depressants*

We also found that 27% of oxycodone ER initiators were co-prescribed at least one CNS depressant, and 4% were co-prescribed at least two CNS depressants (Table 4.2). These study results raise questions about the propriety of this co-prescribing, especially for those residents receiving multiple CNS depressants, because the FDA-approved labeling cautions against the co-prescribing of CNS depressants, particularly in the elderly.<sup>18</sup> Hypnotics, antiemetics, and muscle relaxants were the most frequently co-prescribed with oxycodone ER (Table 4.4). FDA has approved hypnotics for sleep,<sup>36</sup> antiemetics for severe nausea and vomiting, as well as schizophrenia,<sup>37</sup> and muscle relaxants for acute musculoskeletal conditions.<sup>38</sup> These drugs on their own can pose safety risks to elderly patients, including from sedation, respiratory depression, and other adverse effects.<sup>36-38</sup> A recent study found that non-benzodiazepine hypnotics may also increase the risk for hip fractures (from falls) in nursing home residents.<sup>39</sup>

Treatment decisions for nursing home residents are based, in part, on medical judgment and the availability of treatment options.<sup>5</sup> Importantly, there are usually alternative therapies for the conditions treated by these CNS depressant drugs, such as insomnia<sup>40</sup> and schizophrenia.<sup>41</sup> In addition, if a CNS depressant is medically necessary, there are therapies for persistent pain (other than oxycodone ER) that would not interact with the CNS depressant.<sup>4,42,43</sup> Thus, it seems unlikely that the co-prescribing of

oxycodone ER and another CNS depressant was necessary for over one-quarter of residents, but this question should be investigated further.

Some nursing home prescribing practices appear to follow FDA's cautions about co-prescribing. Sedatives were one of the least prescribed drug categories, except for buspirone, and there were almost no prescriptions for first generation antipsychotics or benzodiazepines (Table 4.4). The FDA labeling, though, is not the critical catalyst for this practice. Instead, by the time of our study period, CMS had ceased payment authorizations for benzodiazepines under the Part D program.<sup>39</sup> In addition, typical antipsychotic use was already infrequently prescribed (<2%) in nursing home residents, regardless of opioid prescribing.<sup>44</sup> Finally, for 92% of residents co-prescribed a CNS depressant, the oxycodone ER drug was prescribed in the lowest dose range ( $\leq 20$  mg) (Table 4.3), which at least followed FDA precautions that oxycodone ER drugs should be initiated at lower doses in patients who also receive a CNS depressant.<sup>18</sup>

#### *Co-Prescribing of CNS Agents*

Our alternate analysis reinforces the concerns with CNS drug co-prescribing, because we found that nearly 40% of oxycodone ER initiators were co-prescribed at least 2 CNS agents and 10% were co-prescribed at least 3 CNS agents (Table 4.6). This high prevalence of CNS agent co-prescribing with oxycodone ER raises important concerns for potential adverse events. Studies have found that opioid co-prescribing with CNS agents, such as antipsychotics and antidepressants, increase the risk for serious respiratory depression and opioid overdose.<sup>19,20</sup> One study identified this co-prescribing risk even with relatively low daily opioid doses, which suggests that CNS agent co-

prescribing at the lowest oxycodone ER doses in 94% of residents (Table 4.7) may not be sufficient to ensure safety.<sup>19</sup>

Studies have also found that nursing home residents prescribed opioids, antipsychotics, anti-convulsants (sometimes used as mood stabilizers) or antidepressants have an increased risk for adverse events, including neuropsychiatric effects, and falls.<sup>8,9,45,46</sup> We found that 5% of residents were co-prescribed drugs in all three CNS categories with oxycodone ER (Table 4.9). These risks from individual CNS agents are stronger when used in combination (polypharmacy).<sup>20</sup> In addition, our finding that 80% of nursing home residents initiating oxycodone ER were co-prescribed at least 9 drugs raises even broader polypharmacy concerns (Table 4.11). This polypharmacy prevalence for oxycodone ER initiators is twice the estimate for all nursing home residents based on the 2004 National Nursing Home Survey (NNHS).<sup>12</sup> The 3% of residents receiving prescriptions for at least 29 different drugs during the 30-day window raises alarming polypharmacy concerns, even if some of these drugs were not overlapping (e.g., discontinued some drugs before initiating other drugs in the window).

Our finding that 20% of residents were prescribed an antipsychotic, nearly all atypical, is consistent with other recent estimates that 25% of nursing home residents receive antipsychotic drugs.<sup>44</sup> Atypical antipsychotics are frequently used (estimated between 40-86%) for off-label indications, i.e., not the FDA-approved indications for the treatment of schizophrenia and bi-polar disorder.<sup>47,48</sup> In fact, we found that nearly 80% of the residents initiating oxycodone ER and prescribed antipsychotics had not been diagnosed with schizophrenia or bipolar disorder, suggesting much of this prescribing was for off-label uses (Table 4.10). A common off-label use for atypical antipsychotics



is the treatment of dementia behavioral symptoms, but FDA has warned of an increased mortality risk from the drugs in these patients.<sup>44</sup>

#### *Factors Associated with CNS Depressant Co-Prescribing*

In the multivariate regression analysis, we found that increasing age and cognitive impairment was statistically significantly associated with lower odds for co-prescribing in one CNS depressant category (Table 4.13). This finding contradicted our hypothesis of an opposite effect and suggests that nursing homes are more compliant with the FDA warning against CNS depressant co-prescribing for older and more cognitively impaired residents. Some studies have indicated that advanced age is not a risk factor for inappropriate drug prescribing,<sup>7</sup> and that polypharmacy risks (for greater number of medications) are lower for older and more cognitively impaired nursing home residents.<sup>49</sup> Our analysis also found that Black residents had statistically significant lower odds for CNS depressant co-prescribing, which also contradicts our hypothesis of worse nursing home care for minority residents. This finding, though, is consistent with one study identifying lower odds of medication polypharmacy for Black nursing home residents.<sup>12</sup>

#### *Sensitivity Analysis*

In our sensitivity analysis, assessing the odds for co-prescribing in two or more CSN depressant categories, we found statistically significant associations for increasing age, moderate-severe cognitive impairment, and Black race with decreased odds for co-prescribing that were even stronger than the main model results (Table S4.A). In addition, male residents had half the odds for co-prescribing as women, which is consistent with studies finding that female nursing home residents have higher odds for polypharmacy. These findings suggest that residents who are younger (65-74 years),

more cognitively intact, and White are even more likely to have co-prescribing with two or more depressants, but this association must be investigated further.

*Alternate Analysis: Factors Associated with CNS Agent Co-Prescribing*

Our alternate analysis with the broader CNS agent categories found similar results that increasing age had statistically significantly lower odds for CNS agent co-prescribing (Table S4.B). However, the analysis also found that increasing cognitive impairment had higher odds for this co-prescribing, which is consistent with our hypothesis. This result is the opposite from the main model assessing CNS depressant co-prescribing and means that residents initiating oxycodone ER with greater cognitive impairment are more likely to receive antidepressants, atypical antipsychotics, and/or mood stabilizers, but less likely to receive CNS depressants.

Although treated as a confounder in our model, we also found that increasing MDS mood scale scores were associated with higher odds for co-prescribing with 3 or more CNS agents (Table S4.B). Most strikingly, the highest MDS mood scale score, corresponding with the greatest degree of mood disturbances and agitation, had nearly 4 times the odds for CNS agent co-prescribing. This association is independent of the resident's diagnosis for those mental health conditions included in the model. This finding raises important concerns that mood disturbance behaviors (independent of a mental health diagnosis) may be a factor in the co-prescribing of 3 or more CNS agents with oxycodone ER initiation, particularly for those residents who did not have any pain at their last assessment. One study using the 2004 NNHS survey found that depressed mood indicators and behavioral symptoms were positively associated with antipsychotic drug prescribing in nursing home residents.<sup>44</sup> Many recent public health initiatives have

focused on the inappropriate use of pharmaceuticals to sedate nursing home residents.<sup>2,48</sup>

Our study's finding about mood disturbance and CNS agent co-prescribing should be investigated further.

### *Implications*

Our research findings demonstrate the need for policy makers and practitioners to consider further steps to ensure the appropriate use of oxycodone ER in nursing home residents. The finding that 28.5% of residents initiating oxycodone ER did not have any recorded pain raises important questions about FDA's regulation of extended-release opioids, particularly whether the approved labeling's cautionary statements are sufficient to ensure oxycodone ER's safe use in nursing homes. Furthermore, the co-prescribing of at least 2 different types of CNS agents in 40% of residents, and at least three different types of CNS agents in 10% of residents, illuminates the extent of co-prescribing risks in nursing homes that are beyond the FDA's approved labeling warning, which only focuses on CNS depressants.

In addition to strengthening and expanding a drug's labeling statements about risks, FDA can incorporate other policy approaches. Since our study's time period, FDA has implemented a Risk Evaluation and Mitigation Strategy (REMS) for long-acting opioids such as oxycodone ER that provides additional precautionary steps for their prescribing, such as healthcare provider training.<sup>50</sup> The REMS plan, though, does not include steps or information beyond the product labeling to ensure appropriate prescribing in the elderly, including nursing home residents. FDA could consider including more specific guidance for proper use in the elderly, such as in the nursing home setting, to assist practitioners.

Other stakeholders have an important role in the appropriate use of oxycodone ER in nursing homes. CMS has federal oversight over nursing home practices. The agency could consider strengthening its guidance about CNS drug co-prescribing and examining this co-prescribing in nursing homes more carefully as part of its inspection program.<sup>14</sup> Nursing homes could also incorporate steps in their practices and procedures to ensure extended-release opioids, such as oxycodone ER, are not prescribed to residents without persistent pain or inappropriately co-prescribed with CNS drugs. Nursing homes might focus first on ensuring that residents without any recorded pain are not prescribed an extended-release opioid.

Many recent efforts have attempted to improve the quality of nursing home pain care and prescribing by multimodal approaches incorporating more accurate pain assessment methods, improved communication between staff and clinicians, options for pharmacological and non-pharmacological treatments, and education and training.<sup>51-53</sup> Inappropriate prescribing in nursing home residents is particularly harmful and challenging to address,<sup>54</sup> but one recent study found an educational intervention for nursing home staff was effective in reducing inappropriate use.<sup>55</sup> Our study has identified specific problems with oxycodone ER prescribing that might be more manageable for nursing homes to target through educational efforts.

### *Strengths and Limitations*

Our study has important strengths. The source population included all nursing home residents in the United States who received an oxycodone ER prescription in 2008, which strengthens the results' generalizability. In addition, we based our measures on comprehensive data for prescribing (Part D), resident traits (MDS), and facility

characteristics (OSCAR). We were also able to examine individual and facility level factors, including SES, and control for potential confounders, including the residents' family support and facilities' compliance with federal law. Our findings about the prevalence of CNS drug co-prescribing are consistent with prior studies in nursing homes and expand on these earlier findings to residents initiating oxycodone ER. In addition, our study analyzes not only CNS depressant use, but also CNS agents more generally, which provides a more complete assessment of nursing home co-prescribing practices with this extended-release opioid.

The study also has important limitations. First, we could not determine the medical reasons for the CNS depressant co-prescribing in residents. There may have been legitimate medical need for this prescribing in many residents, particularly for those residents only prescribed one CNS depressant. We also could not assess if the nursing home closely monitored residents during their CNS depressant co-prescribing, which might help justify the medical decision to initiate the oxycodone ER. Our alternate analysis helps address these limitations, though, because the co-prescribing of CNS drugs in the broader CNS categories, particularly 40% with two categories and 10% with three categories, raises significant safety concerns.

Second, there was a time lag between the last MDS measurement and oxycodone ER initiation date for each resident, which averaged 34 days overall and was greater than 60 days for approximately 20% of the residents. This gap could mean that some residents developed persistent pain after the last MDS assessment that justified the oxycodone ER initiation. However, important changes in resident pain, such as the development of persistent pain requiring a long-acting opioid, would trigger an MDS assessment if

considered a significant change in resident status.<sup>25</sup> To address any misclassification for persistent pain status, we restricted the sample in our sensitivity analysis to those residents with an MDS assessment no more than 30 days prior to oxycodone ER initiation and found similar results as our main analysis.

Third, our persistent pain definition may have misclassified some residents' oxycodone ER initiation as non-adherent to the labeling condition for pain when they actually had continuous, moderate-to-severe pain satisfying this condition. In addition, if nursing home staff underestimated the intensity and/or duration for a resident's pain in the MDS measurement, then our study would have classified incorrectly their fentanyl initiation as non-adherent to the persistent pain condition. However, our finding that 88% of residents did not have persistent pain is so great that misclassification seems unlikely to account for a sufficiently large extent to alleviate our adherence concerns. In addition, our sensitivity analysis showed that at least 20% of residents did not have any pain within 5 days prior to initiating the transdermal fentanyl prescription. This finding is still troubling even with the potential for MDS measurement error.

Finally, the study's cross-sectional nature precludes examining any causal associations between factors and inappropriate oxycodone prescribing. However, we did obtain measurements for the individual factors prior to the oxycodone prescribing, which can alleviate concerns that the opioid prescribing would have affected these resident factors in ways (such as the mood scale score) that might have influenced co-prescribing decisions.

## **CONCLUSION**

We have examined the important public health issue of long-acting opioid prescribing in a large, institutional setting and assessed whether the prescribing follows federal requirements and guidelines. Our findings, from a study population drawn from all nursing home residents in the United States, indicate that a large proportion of residents have received oxycodone ER inappropriately because they were not in persistent pain and were co-prescribed multiple CNS agents. In addition, certain resident factors, particularly being younger and more cognitively impaired, were associated with more frequent co-prescribing of CNS agents (e.g., antidepressant, antipsychotic, and mood stabilizer drugs). These results support the need for FDA, CMS, and nursing homes to take additional steps to better ensure appropriate extended-release opioid prescribing for residents. These public health efforts will be critical to help protect these vulnerable individuals from the unnecessary risks posed by dangerous prescribing practices in nursing homes.

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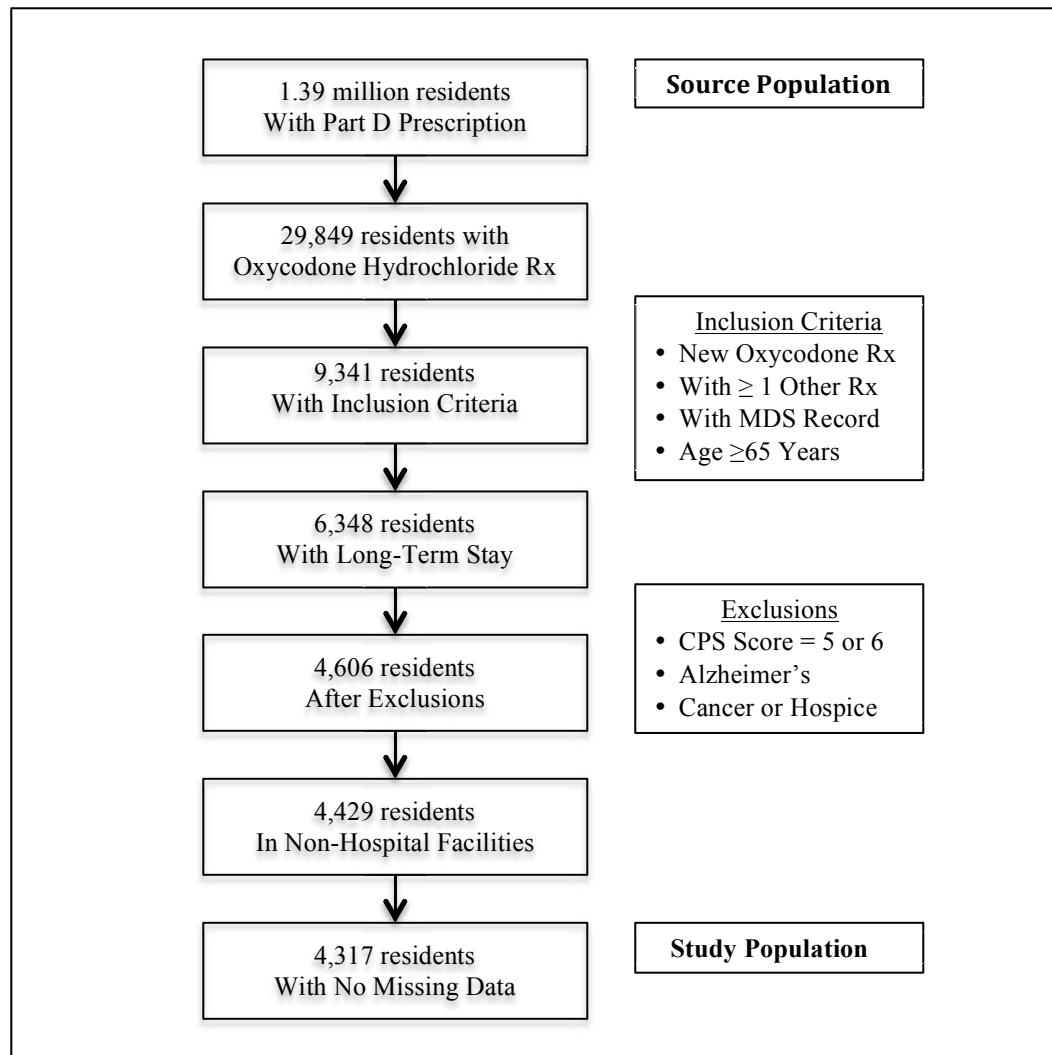
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## Figures and Tables

**Figure 4.1. Oxycodone Hydrochloride ER. Source and Study Populations from Part D and Minimum Data Set (2008).**



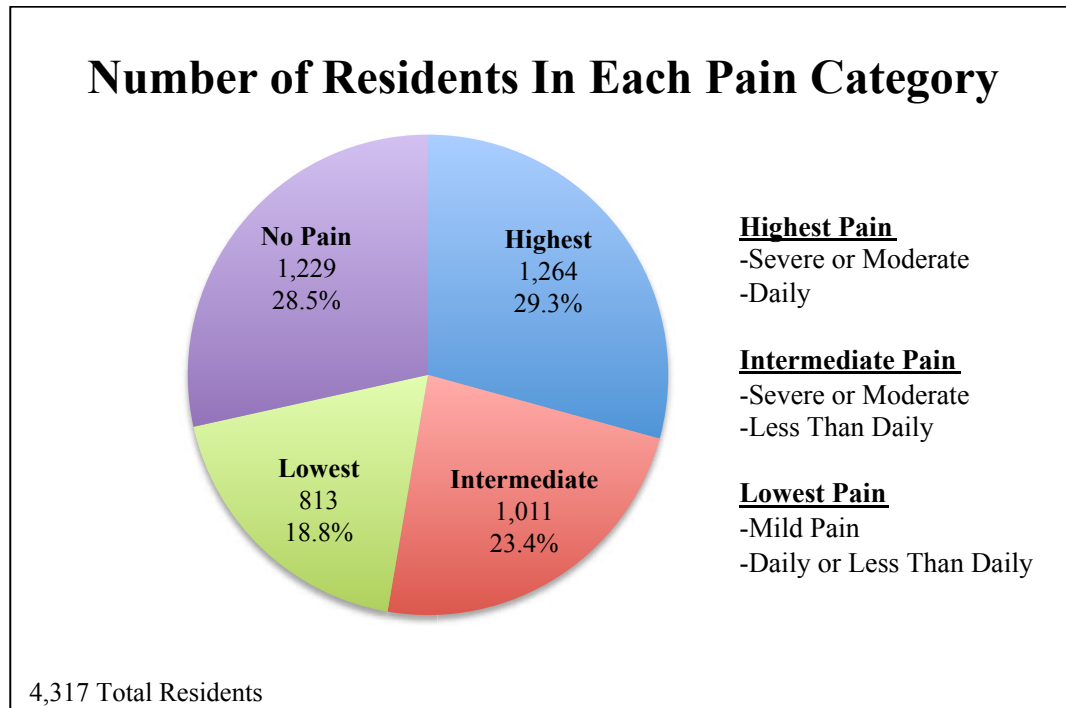
**Figure 4.2a. Central Nervous System (CNS) Depressants.**

<b>Sedatives</b>		
<u>Benzodiazepines</u>	<u>Buspirone</u>	<u>Barbiturates</u>
alprazolam	buspirone	amobarbital
chlordiazepoxide		pentobarbital
clonazepam		phenobarbital
clorazepate		secobarbital
diazepam		
lorazepam		
oxazepam		
<b>Hypnotics</b>		
<u>Benzodiazepines</u>	<u>Non-Benzodiazepines</u>	
flurazepam	eszopiclone	
temazepam	zaleplon	
triazolam	zolpidem	
	zopiclone	
<b>Antipsychotics (Atypical)</b>		<b>Muscle Relaxants</b>
chlorpromazine		baclofen
fluphenazine		carisoprodol
perphenazine		chlorzoxazone
thioridazine		cyclobenzaprine
trifluoperazine		dantrolene
		metaxalone
<b>Antiemetics</b>		orphenadrine
prochlorperazine		tizanidine
promethazine		

**Figure 4.2b. Central Nervous System (CNS) Agents.**

<b>Antidepressants</b>			
amitriptyline	escitalopram	paroxetine	
amoxapine	fluoxetine	paroxetine mesylate	
bupropion	fluvoxamine	phenelzine	
citalopram	imipramine	protriptyline	
clomipramine	imipramine pamoate	selegiline	
desipramine	isocarboxazid	sertraline	
desvenlafaxine	maprotiline	tranylcypromine	
doxepin	mirtazapine	trazodone	
duloxetine	notriptyline	trimipramine	
		venlafaxine	
<b>Antipsychotics</b>			
<u>Typical</u>	<u>Atypical</u>	<u>Atypical (cont.)</u>	<u>Atypical (cont.)</u>
chlorpromazine	aripiprazole	loxapine	pimozide
fluphenazine	clozapine	lurasidone	quetiapine
perphenazine	fluoxetine-olanzapine	molindone	risperidone
thioridazine	haloperidol	olanzapine	thiothixene
trifluoperazine	iloperidone	paliperidone	ziprasidone
<b>Anti-Anxiety Drugs</b>			
<u>Benzodiazepines</u>	<u>Buspirone</u>		
alprazolam	buspirone		
chlordiazepoxide			
clonazepam			
clorazepate			
diazepam			
lorazepam			
oxazepam			
<b>Mood Stabilizers</b>	<b>Muscle Relaxants</b>		
carbamazepine	baclofen		
divalproex sodium	carisoprodol		
gabapentin	chlorzoxazone		
lamotrigine	cyclobenzaprine		
lithium	dantrolene		
oxcarbazepine	metaxalone		
topiramate	orphenadrine		
	tizanidine		

**Figure 4.3. Number of Residents in Different Pain Categories at Last Assessment Before Oxycodone Hydrochloride ER Initiation.**





**Table 4.1. Numbers of Residents Initiating Oxycodone Hydrochloride ER Persistent Pain and Co-Prescribed at Least 1 CNS Depressant (n=4,317)\***

<b>Persistent Pain</b>	<b>CNS Depressant Co-Prescribed</b>			<b>Total Population</b>
		<b>No N (%)</b>	<b>Yes N (%)</b>	
	<b>No N (%)</b>	2,836 (65.7)	965 (22.4 )	3,801 (88.1)
	<b>Yes N (%)</b>	334 (7.7)**	182 (4.2)	516 (12.0)
	<b>Total Population</b>	3,170 (73.4)	1,147 (26.6)	4,317 (100)***

\*All percentages are based on total population of 4,317 residents in denominator.

\*\*Oxycodone Hydrochloride ER prescribing adhered to labeling condition for persistent pain and warnings against concomitant CNS depressant medication.

\*\*\*Percentages do not add to 100 due to rounding.

**Table 4.2. CNS Depressants: Total Number of Categories with Drugs Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER (n=4,317).**

<b>Number of Categories Prescribed</b>	<b>Number of Residents (Percentage)</b>
0	3,170 (73.4)
1	978 (22.7)
2	155 (3.6)
3	13 (0.3)
≥4	1 (0.02)

**Table 4.3. Dosage Strength of Oxycodone Hydrochloride ER by Co-Prescribing Status.**

<b>Oxycodone Hydrochloride ER Strength</b>	<b>CNS Depressant Co-Prescribing</b>			<b>Total</b>
		<b>Yes N (%)</b>	<b>No N (%)</b>	
	<b>Lower (≤20 mg) N (%)</b>	1,054 (91.9)	3,005 (94.8)	4,059 (94.0)
	<b>Higher(&gt;20 mg) N (%)</b>	93 (8.1)	165 (5.2)	258 (6.0)
	<b>Total</b>	1,147	3,170	4,317

**Table 4.4. CNS Depressants Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER: By Category (n=4,317).**

<b>CNS Depressant Category</b>	<b>Number of Residents (Percentage)*</b>
Hypnotic	488 (11.3)
• Non-Benzodiazepine	482 (11.2)
• Benzodiazepine	7 (0.2)
Muscle Relaxant	372 (8.6)
Antiemetic	323 (7.5)
Sedative	122 (2.8)
• Buspirone	103 (2.4)
• Benzodiazepine	21 (0.5)
• Barbiturates	0 (0.0)
First Generation Antipsychotic	26 (0.6)

\* Category sums exceed 1,147 total because of overlapping prescriptions for individuals.

**Table 4.5. CNS Depressant Category Combinations: Drugs Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER (n=4,317).**

<b>CNS Depressant Combinations</b>	<b>Number of Residents (Percentage)*</b>
<b>No CNS Depressants</b>	<b>3,170 (73.4)</b>
<b>1 CNS Depressant Only</b>	<b>978 (22.7)</b>
• Hypnotic	365 (8.5)
• Muscle Relaxant	279 (6.5)
• Antiemetic	231 (5.4)
• Sedative	83 (1.9)
• First Generation Antipsychotic	20 (0.5)
<b>2 CNS Depressants</b>	<b>155 (3.6)</b>
• Hypnotic	49 (1.1)
• Muscle Relaxant	49 (1.1)
• Hypnotic	48 (1.1)
• Antiemetic	48 (1.1)
• Antiemetic	24 (0.6)
• Muscle Relaxant	24 (0.6)
<b>3 CNS Depressants</b>	<b>13 (0.3)</b>
<b>4 CNS Depressants</b>	<b>1 (0.02)</b>

\* Only included combinations >0.5% of population.

**Table 4.6. CNS Agents: Total Number of Categories with Drugs Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER (n=4,317).**

Number of Categories Prescribed	Number of Residents (Percentage)
0	716 (16.6)
1	1,961 (45.4)
2	1,209 (28.0)
3	382 (8.9)
4	48 (1.1)
5	1 (0.02)

**Table 4.7. Dosage Strength of Oxycodone Hydrochloride ER by Co-Prescribing Status.**

		CNS Agent Co-Prescribing (≥2 CNS Agents)		Total
		Yes N (%)	No N (%)	
Oxycodone Hydrochloride ER Strength	Lower (≤20 mg) N (%)	1,549 (94.5)	2,510 (93.8)	4,059 (94.0)
	Higher(>20 mg) N (%)	91 (5.5)	167 (6.2)	258 (6.0)
	Total	1,640	2,677	4,317

**Table 4.8. CNS Agents Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER: By Category (n=4,317).**

CNS Agent Category	Number of Residents (Percentage)*
Antidepressant	3,107 (72.0)
Mood Stabilizer	1,271 (29.4)
Antipsychotic	850 (19.7)
• Second Generation	834 (19.3)
• First Generation	26 (0.6)
Muscle Relaxant	372 (8.6)
Anti-Anxiety	122 (2.8)
• Buspirone	103 (2.4)
• Benzodiazepine	21 (0.5)

\* Category sums exceed 3,601 total because of overlapping prescriptions for individuals.

**Table 4.9. CNS Agent Category Combinations: Drugs Co-Prescribed for Residents Initiating Oxycodone Hydrochloride ER (n=4,317).**

<b>CNS Agent Combinations</b>	<b>Number of Residents (Percentage)*</b>
<b>No CNS Agents</b>	<b>716 (16.6)</b>
<b>1 CNS Agent Only</b>	<b>1,961 (45.4)</b>
<ul style="list-style-type: none"> <li>• Antidepressant</li> <li>• Mood Stabilizer</li> <li>• Antipsychotic</li> <li>• Muscle Relaxant</li> <li>• Anti-Anxiety</li> </ul>	1,560 (36.1) 228 (5.3) 106 (2.5) 54 (1.3) 13 (0.3)
<b>2 CNS Agents</b>	<b>1,209 (28.0)</b>
<ul style="list-style-type: none"> <li>• Antidepressant</li> <li>• Mood Stabilizer</li> <li>• Antidepressant</li> <li>• Antipsychotic</li> <li>• Antidepressant</li> <li>• Muscle Relaxant</li> <li>• Antipsychotic</li> <li>• Mood Stabilizer</li> <li>• Antidepressant</li> <li>• Anti-Anxiety</li> </ul>	593 (13.8) 365 (8.5) 124 (2.9) 55 (1.3) 43 (1.0)
<b>3 CNS Agents</b>	<b>382 (8.9)</b>
<ul style="list-style-type: none"> <li>• Antidepressant</li> <li>• Antipsychotic</li> <li>• Mood Stabilizer</li> <li>• Antidepressant</li> <li>• Mood Stabilizer</li> <li>• Muscle Relaxant</li> <li>• Antidepressant</li> <li>• Antipsychotic</li> <li>• Muscle Relaxant</li> </ul>	215 (5.0) 83 (1.9) 35 (0.8)
<b>4 CNS Agents</b>	<b>48 (1.1)</b>
<ul style="list-style-type: none"> <li>• Antidepressant</li> <li>• Antipsychotic</li> <li>• Mood Stabilizer</li> <li>• Muscle Relaxant</li> </ul>	28 (0.7)
<b>5 CNS Agents</b>	<b>1 (0.02)</b>

\* Only included combinations >0.5% of population.

**Table 4.10. Prescribing of Antipsychotics for Off-Label Uses During 30-Day Window After Oxycodone Hydrochloride ER Initiation (n=4,377).**

		Antipsychotic Prescription		Total
		Yes N (%)	No N (%)	
Bipolar Disorder or Schizophrenia Diagnosis	Yes	180 (21.2)	76 (2.2)	256
	No	670 (78.8)	3,391 (97.8)	4,051
	Total	850	3,467	4,317

**Table 4.11. Total Number of Drugs Prescribed During 30-Day Window After Oxycodone Hydrochloride ER Initiation (n=4,317).**

Categories	Number of Residents (Percentage)
1-4 Drugs	149 (3.5)
5-8 Drugs	725 (16.8)
9-12 Drugs	1,392 (32.2)
13-16 Drugs	1,067 (24.7)
17-20 Drugs	556 (12.9)
21-24 Drugs	208 (4.8)
25-28 Drugs	74 (1.7)
≥29 Drugs	146 (3.4)
<b>Total</b>	<b>4,317</b>

**Table 4.12. Characteristics of Nursing Home Residents by CNS Depressant Co-Prescribing within 30 Days After Oxycodone Hydrochloride ER Initiation (n=4,317).\***

	No CNS Depressant Co- Prescribing N (%)**	CNS Depressant Co-Prescribing (1 or More Rx) N (%)**	X <sup>2</sup> Statistic p Value***
<b>Total Population</b>	3,170 (73.4)	1,147 (26.6)	
<b>Characteristics</b>			
Gender			0.496
Female	2,434 (76.8)	892 (77.8)	
Male	736 (23.2)	255 (22.2)	
Age			<0.001
65-74	671 (21.2)	380 (33.1)	
75-84	1,159 (36.6)	450 (39.2)	
85-94	1,161 (36.6)	290 (25.3)	
≥95	179 (5.7)	27 (2.4)	
Race			0.051
White	2,789 (88.0)	1,037 (90.4)	
Black	264 (8.3)	69 (6.0)	
Hispanic	80 (2.5)	32 (2.8)	
Other	37 (1.2)	9 (0.8)	
Cognitive Impairment by CPS Score			<0.001
Intact=0	772 (24.4)	396 (34.5)	
Borderline	542 (17.1)	244 (21.3)	
Intact=1			
Mild	675 (21.3)	226 (19.7)	
Impairment=2			
Moderate	989 (31.2)	251 (21.9)	
Impairment=3			
Moderate-Severe	192 (6.1)	30 (2.6)	
Impairment=4			
Resident Self-Pay			0.002
No	2,717 (85.7)	1,025 (89.4)	
Yes	453 (14.3)	122 (10.6)	
Education Level			0.467
< High School Graduate	1,086 (34.3)	376 (32.8)	
High School Graduate	1,848 (58.3)	675 (58.9)	
College Graduate	236 (7.4)	96 (8.4)	
Facility Average Staff Hours Per Resident			0.490
<2.5 Hours	118 (3.7)	46 (4.0)	
2.5-3.0 Hours	365 (11.5)	141 (12.3)	
3.0-3.5 Hours	963 (30.4)	371 (32.4)	
3.5-4.0 Hours	948 (29.9)	309 (26.9)	
4.0-4.5 Hours	472 (14.9)	166 (14.5)	
>4.5 Hours	304 (9.6)	114 (9.9)	

Facility's Proportion of Residents Self-Pay			<0.001
<10%	387 (12.2)	154 (13.4)	
10-30%	1,833 (57.8)	736 (64.2)	
30-50%	778 (24.5)	215 (18.7)	
>50%	172 (5.4)	42 (3.7)	
Facility For Profit			<0.001
No	1,094 (34.5)	336 (29.3)	
Yes	2,076 (65.5)	811 (70.7)	
ADL Help: Morris Additive Scale			0.199
0 ADLs	149 (4.7)	71 (6.2)	
1-7 ADLs	438 (13.8)	174 (15.2)	
8-14 ADLs	654 (20.6)	223 (19.4)	
15-21 ADLs	1,362 (43.0)	472 (41.2)	
22-28 ADLs	567 (17.9)	207 (18.1)	
MDS Mood Scale			0.592
0	1,811 (57.1)	654 (57.0)	
1-2	696 (22.0)	240 (20.9)	
3-4	474 (15.0)	170 (14.8)	
5-6	165 (5.2)	74 (6.5)	
7-8	24 (0.8)	9 (0.8)	
Family Support			0.004
No	1,744 (55.0)	687 (59.9)	
Yes	1,426 (45.0)	460 (40.1)	
Facility Compliant with Federal Law			0.566
Yes	2,876 (90.7)	1,034 (90.2)	
No	294 (9.3)	113 (9.9)	
Persistent Pain			<0.001
No	2,836 (89.5)	965 (84.1)	
Yes	334 (10.5)	182 (15.9)	
Mental Health Condition****			<0.001
No	941 (29.7)	274 (23.9)	
Yes	2,229 (70.3)	873 (76.1)	

Notes: Due to rounding, percentages do not all sum to 100. ADL=Activities of Daily Living.  
CPS=Cognitive Performance Scale.

\* Excludes 112 (2.6%) observations with missing values.

\*\* All percentages correspond to row totals.

\*\*\* p value corresponds to the  $X^2$  statistic.

\*\*\*\* Mental Health Condition. Resident has at least one of the following diagnosed conditions: depression, anxiety disorder, bipolar disorder, or schizophrenia.

**Table 4.13. Odds Ratios for Co-Prescribing of At Least 1 Central Nervous System (CNS) Depressant with Oxycodone Hydrochloride ER Initiation.\***

Univariate Models** (n=4,317)				Multivariate Model*** (n=4,317)		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	0.94	0.80-1.12	0.504	0.86	0.72-1.02	0.085
Age						
65-74	(Ref)			(Ref)		
75-84	<b>0.70</b>	<b>0.58-0.83</b>	<b>&lt;0.001</b>	<b>0.77</b>	<b>0.64-0.92</b>	<b>0.005</b>
85-94	<b>0.45</b>	<b>0.37-0.55</b>	<b>&lt;0.001</b>	<b>0.52</b>	<b>0.43-0.64</b>	<b>&lt;0.001</b>
≥95	<b>0.28</b>	<b>0.18-0.44</b>	<b>&lt;0.001</b>	<b>0.38</b>	<b>0.24-0.60</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	<b>0.64</b>	<b>0.48-0.86</b>	<b>0.003</b>	<b>0.60</b>	<b>0.44-0.81</b>	<b>0.001</b>
Hispanic	1.02	0.66-1.60	0.915	0.97	0.61-1.53	0.896
Asian	0.57	0.26-1.23	0.151	0.65	0.29-1.43	0.282
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	0.88	0.71-1.08	0.395	0.89	0.73-1.10	0.289
Intact=1						
Mild	<b>0.65</b>	<b>0.53-0.80</b>	<b>&lt;0.001</b>	<b>0.71</b>	<b>0.57-0.88</b>	<b>0.002</b>
Impairment=2						
Moderate	<b>0.48</b>	<b>0.40-0.59</b>	<b>&lt;0.001</b>	<b>0.52</b>	<b>0.42-0.65</b>	<b>&lt;0.001</b>
Impairment=3						
Moderate-Severe	<b>0.30</b>	<b>0.20-0.46</b>	<b>&lt;0.001</b>	<b>0.32</b>	<b>0.21-0.49</b>	<b>&lt;0.001</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>0.74</b>	<b>0.59-0.93</b>	<b>0.009</b>	0.89	0.70-1.13	0.341
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.06	0.91-1.24	0.433	0.98	0.83-1.15	0.803
Graduate						
College Graduate	1.20	0.91-1.58	0.207	1.14	0.85-1.52	0.374
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	1.02	0.67-1.54	0.943	1.03	0.67-1.58	0.898
3.0-3.5 Hours	1.15	0.78-1.71	0.473	1.18	0.79-1.76	0.417
3.5-4.0 Hours	1.01	0.68-1.50	0.974	1.05	0.70-1.58	0.824
4.0-4.5 Hours	1.01	0.66-1.54	0.960	1.15	0.75-1.78	0.519
>4.5 Hours	1.03	0.66-1.59	0.910	1.18	0.75-1.86	0.471



Univariate Models (continued)				Multivariate Model (continued)		
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	1.07	0.86-1.33	0.540	1.07	0.85-1.35	0.553
30-50%	0.78	0.60-1.02	0.069	0.85	0.64-1.12	0.253
>50%	<b>0.65</b>	<b>0.43-0.98</b>	<b>0.039</b>	0.74	0.48-1.14	0.173
Facility For Profit						
No	(Ref)					
Yes	1.11	0.94-1.31	0.210	0.98	0.82-1.16	0.784
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	0.78	0.55-1.11	0.172	0.91	0.63-1.30	0.592
8-14 ADLs	<b>0.66</b>	<b>0.47-0.92</b>	<b>0.016</b>	0.85	0.60-1.21	0.373
15-21 ADLs	<b>0.72</b>	<b>0.52-0.98</b>	<b>0.040</b>	0.93	0.67-1.29	0.664
22-28 ADLs	0.73	0.52-1.03	0.073	1.08	0.76-1.55	0.664
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.98	0.82-1.18	0.860	1.01	0.84-1.22	0.934
3-4	1.04	0.84-1.28	0.715	1.05	0.85-1.30	0.664
5-6	<b>1.37</b>	<b>1.01-1.86</b>	<b>0.045</b>	<b>1.58</b>	<b>1.15-2.18</b>	<b>0.005</b>
7-8	1.17	0.52-2.63	0.707	1.50	0.65-3.45	0.337
Family Support						
No	(Ref)			(Ref)		
Yes	<b>0.84</b>	<b>0.73-0.97</b>	<b>0.018</b>	0.92	0.79-1.06	0.255
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	1.00	0.77-1.30	0.990	0.96	0.74-1.26	0.790
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>1.51</b>	<b>1.22-1.85</b>	<b>&lt;0.001</b>	<b>1.28</b>	<b>1.03-1.58</b>	<b>0.025</b>
Mental Health Condition****						
No	(Ref)			(Ref)		
Yes	<b>1.33</b>	<b>1.13-1.56</b>	<b>0.001</b>	1.18	1.00-1.40	0.057

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Central nervous system depressants are any sedative, typical antipsychotic, hypnotic, antiemetic, as well as muscle relaxant drugs.

\*\* Univariate Logistic Models. This column presents the univariate logistic model results for each individual variable, unadjusted for the other variables.

\*\*\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; resident persistent pain; and at least one mental health diagnosis.

\*\*\*\* Mental Health Condition. Resident has at least one of the following diagnosed conditions: depression, anxiety disorder, bipolar disorder, or schizophrenia.

All regressions used multi-level modeling at the state and facility levels.

**Appendix S4.A. Sensitivity Analyses. Odds Ratios for Co-Prescribing Central Nervous System (CNS) Depressant with Oxycodone Hydrochloride ER Initiation.\***

	<b>Model 1: Keep Only Residents with MDS Visit within 30 days prior to Oxycodone ER Initiation (n=2,215)</b>			<b>Model 2: Alternative Outcome CNS Depressant Co-Prescribing (≥2 CNS Depressants)** (n=4,317)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	0.85	0.67-1.08	0.195	<b>0.48</b>	<b>0.30-0.77</b>	<b>0.002</b>
Age						
65-74	(Ref)			(Ref)		
75-84	0.81	0.64-1.04	0.096	<b>0.52</b>	<b>0.35-0.78</b>	<b>0.001</b>
85-94	<b>0.49</b>	<b>0.37-0.65</b>	<b>&lt;0.001</b>	<b>0.27</b>	<b>0.16-0.46</b>	<b>&lt;0.001</b>
≥95	<b>0.39</b>	<b>0.21-0.72</b>	<b>0.003</b>	<b>0.08</b>	<b>0.01-0.59</b>	<b>0.014</b>
Race						
White	(Ref)			(Ref)		
Black	<b>0.55</b>	<b>0.37-0.83</b>	<b>0.004</b>	<b>0.27</b>	<b>0.10-0.72</b>	<b>0.008</b>
Hispanic	0.80	0.43-1.50	0.483	0.83	0.27-2.54	0.746
Other	0.70	0.27-1.86	0.479	1.25	0.25-6.23	0.786
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	0.91	0.69-1.21	0.533	0.93	0.59-1.47	0.764
Intact=1						
Mild	<b>0.75</b>	<b>0.56-0.99</b>	<b>0.042</b>	0.66	0.40-1.09	0.106
Impairment=2						
Moderate	<b>0.48</b>	<b>0.36-0.64</b>	<b>&lt;0.001</b>	<b>0.50</b>	<b>0.30-0.84</b>	<b>0.009</b>
Impairment=3						
Moderate-Severe	<b>0.22</b>	<b>0.11-0.42</b>	<b>&lt;0.001</b>	<b>0.19</b>	<b>0.04-0.83</b>	<b>0.027</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	0.99	0.72-1.37	0.974	1.10	0.62-1.95	0.746
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.05	0.85-1.31	0.638	1.18	0.80-1.74	0.391
Graduate						
College Graduate	1.20	0.80-1.81	0.377	0.96	0.47-1.97	0.914

Model 1 (continued)				Model 2 (continued)		
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	1.30	0.69-2.42	0.682	0.77	0.30-1.99	0.595
3.0-3.5 Hours	1.23	0.68-2.23	0.999	0.87	0.36-2.07	0.745
3.5-4.0 Hours	1.30	0.71-2.37	0.556	0.92	0.38-2.22	0.849
4.0-4.5 Hours	1.28	0.68-2.41	0.687	0.95	0.37-2.48	0.921
>4.5 Hours	1.60	0.84-3.07	0.350	1.05	0.39-2.83	0.923
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	1.10	0.81-1.49	0.551	1.13	0.67-1.91	0.638
30-50%	0.92	0.63-1.35	0.668	0.66	0.33-1.30	0.226
>50%	1.13	0.65-1.97	0.655	0.71	0.24-2.15	0.548
Facility For Profit						
No	(Ref)			(Ref)		
Yes	0.99	0.78-1.27	0.966	1.15	0.74-1.77	0.540
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	0.70	0.43-1.16	0.168	0.73	0.36-1.47	0.379
8-14 ADLs	0.63	0.39-1.01	0.054	0.50	0.24-1.02	0.057
15-21 ADLs	0.75	0.48-1.18	0.211	0.55	0.28-1.05	0.071
22-28 ADLs	0.92	0.57-1.50	0.746	0.87	0.42-1.77	0.692
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.94	0.72-1.22	0.633	<b>0.49</b>	<b>0.29-0.81</b>	<b>0.005</b>
3-4	0.99	0.73-1.33	0.924	0.79	0.47-1.30	0.353
5-6	1.26	0.81-1.95	0.303	1.50	0.76-2.95	0.242
7-8	1.05	0.32-3.44	0.942	0.93	0.11-8.15	0.946
Family Support						
No	(Ref)			(Ref)		
Yes	0.91	0.74-1.12	0.376	1.21	0.85-1.72	0.289
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	1.07	0.75-1.52	0.712	0.74	0.39-1.41	0.367
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>1.37</b>	<b>1.03-1.82</b>	<b>0.029</b>	<b>1.88</b>	<b>1.23-2.86</b>	<b>0.003</b>
Mental Health Condition***						
No	(Ref)			(Ref)		
Yes	1.15	0.91-1.44	0.250	1.12	0.74-1.69	0.585

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; resident persistent pain, and at least one mental health diagnosis.

\*\* Central nervous system depressants are any sedative, typical antipsychotic, hypnotic, antiemetic, as well as muscle relaxant drugs.

\*\*\* Mental Health Condition. Resident has at least one of the following diagnosed conditions: depression, anxiety disorder, bipolar disorder, or schizophrenia.

All regressions used multi-level modeling at the state and facility levels.

**Appendix S4.B. Alternate Analyses.\* Odds Ratios for Central Nervous System (CNS) Agent Co-Prescribing with Oxycodone Hydrochloride ER Initiation.\*\***

	<b>Model 1: Odds Ratio for ≥ 2 CNS Agents Co-Prescribed (n=4,317)</b>			<b>Model 2: Odds Ratio for ≥ 3 CNS Agents Co-Prescribed (n=4,317)</b>		
	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>	<b>Odds Ratio</b>	<b>95% CI</b>	<b>p-Value</b>
<b>Characteristics</b>						
Gender						
Female	(Ref)			(Ref)		
Male	<b>0.82</b>	<b>0.70-0.96</b>	<b>0.015</b>	0.89	0.69-1.14	0.357
Age						
65-74	(Ref)			(Ref)		
75-84	<b>0.69</b>	<b>0.58-0.81</b>	<b>&lt;0.001</b>	<b>0.53</b>	<b>0.42-0.68</b>	<b>&lt;0.001</b>
85-94	<b>0.39</b>	<b>0.33-0.47</b>	<b>&lt;0.001</b>	<b>0.33</b>	<b>0.25-0.45</b>	<b>&lt;0.001</b>
≥95	<b>0.22</b>	<b>0.15-0.33</b>	<b>&lt;0.001</b>	<b>0.12</b>	<b>0.04-0.32</b>	<b>&lt;0.001</b>
Race						
White	(Ref)			(Ref)		
Black	0.82	0.63-1.06	0.128	0.69	0.45-1.06	0.092
Hispanic	0.89	0.59-1.35	0.590	0.59	0.28-1.24	0.162
Other	1.31	0.69-2.49	0.415	0.81	0.28-2.37	0.697
Cognitive Impairment by CPS Score						
Intact=0	(Ref)			(Ref)		
Borderline	1.19	0.97-1.45	0.092	1.25	0.91-1.72	0.173
Intact=1						
Mild	1.20	0.99-1.46	0.068	1.28	0.93-1.76	0.126
Impairment=2						
Moderate	<b>1.43</b>	<b>1.19-1.73</b>	<b>&lt;0.001</b>	<b>1.56</b>	<b>1.15-2.11</b>	<b>0.004</b>
Impairment=3						
Moderate-Severe	<b>1.70</b>	<b>1.22-2.35</b>	<b>0.002</b>	<b>1.66</b>	<b>1.00-2.73</b>	<b>0.049</b>
Impairment=4						
Resident Self-Pay						
No	(Ref)			(Ref)		
Yes	<b>0.80</b>	<b>0.65-0.99</b>	<b>0.042</b>	0.74	0.51-1.09	0.126

	Model 1 (continued)			Model 2 (continued)		
Education Level						
<High School	(Ref)			(Ref)		
Graduate						
High School	1.04	0.90-1.20	0.598	1.10	0.87-1.38	0.425
Graduate						
College Graduate	1.20	0.92-1.56	0.183	1.22	0.81-1.84	0.330
Facility Average Staff Hours Per Resident						
<2.5 Hours	(Ref)			(Ref)		
2.5-3.0 Hours	0.87	0.59-1.28	0.476	<b>0.51</b>	<b>0.31-0.84</b>	<b>0.008</b>
3.0-3.5 Hours	0.82	0.57-1.17	0.270	<b>0.45</b>	<b>0.29-0.71</b>	<b>0.001</b>
3.5-4.0 Hours	0.81	0.56-1.16	0.240	<b>0.41</b>	<b>0.26-0.64</b>	<b>&lt;0.001</b>
4.0-4.5 Hours	0.91	0.62-1.33	0.621	<b>0.42</b>	<b>0.25-0.70</b>	<b>0.001</b>
>4.5 Hours	0.98	0.66-1.46	0.915	<b>0.49</b>	<b>0.29-0.84</b>	<b>0.009</b>
Facility's Proportion of Residents Self-Pay						
<10%	(Ref)			(Ref)		
10-30%	1.07	0.87-1.31	0.533	0.96	0.71-1.30	0.807
30-50%	0.88	0.69-1.12	0.304	0.75	0.52-1.09	0.134
>50%	0.93	0.64-1.36	0.709	0.67	0.34-1.32	0.249
Facility For Profit						
No	(Ref)			(Ref)		
Yes	1.16	0.99-1.36	0.061	1.10	0.86-1.41	0.438
ADL Help: Morris Additive Scale						
0 ADLs	(Ref)			(Ref)		
1-7 ADLs	1.04	0.74-1.46	0.820	0.98	0.57-1.66	0.931
8-14 ADLs	0.91	0.65-1.26	0.560	0.79	0.47-1.34	0.379
15-21 ADLs	0.95	0.70-1.29	0.734	1.01	0.62-1.64	0.974
22-28 ADLs	0.80	0.57-1.12	0.195	1.08	0.64-1.82	0.783
MDS Mood Scale						
0	(Ref)			(Ref)		
1-2	0.99	0.84-1.18	0.948	1.09	0.83-1.42	0.540
3-4	<b>1.29</b>	<b>1.07-1.56</b>	<b>0.009</b>	1.28	0.96-1.72	0.089
5-6	<b>1.81</b>	<b>1.35-2.43</b>	<b>&lt;0.001</b>	<b>2.01</b>	<b>1.36-2.97</b>	<b>&lt;0.001</b>
7-8	<b>2.60</b>	<b>1.25-5.43</b>	<b>0.011</b>	<b>3.70</b>	<b>1.63-8.39</b>	<b>0.002</b>
Family Support						
No	(Ref)			(Ref)		
Yes	0.89	0.78-1.02	0.083	0.88	0.71-1.09	0.251
Facility Compliant with Federal Law						
Yes	(Ref)			(Ref)		
No	0.97	0.77-1.23	0.813	0.98	0.69-1.38	0.892
Persistent Pain						
No	(Ref)			(Ref)		
Yes	<b>1.25</b>	<b>1.02-1.52</b>	<b>0.030</b>	1.32	0.99-1.76	0.061
Mental Health Condition***						
No	(Ref)			(Ref)		
Yes	<b>2.68</b>	<b>2.28-3.15</b>	<b>&lt;0.001</b>	<b>2.56</b>	<b>1.88-3.49</b>	<b>&lt;0.001</b>

Notes: CI=confidence interval; Ref=reference; ADL=Activities of Daily Living; CPS=Cognitive Performance Scale. Boldface type indicates  $p < 0.05$ .

\* Multivariate Logistic Regression Model. Adjusted for gender; age; race; cognitive functioning; resident self-pay status; education; facility average staff hours per resident; facility percentage of residents who self-pay; facility for-profit status; resident number of activities of daily living (ADLs) on Morris Additive scale requiring help; resident score on MDS mood scale, resident family support; facility compliance with federal law; resident persistent pain, and at least one mental health diagnosis.

\*\* Central nervous system agents are any antidepressant, antipsychotic, anti-anxiety, mood stabilizer, or muscle relaxant drugs.

\*\*\* Mental Health Condition. Resident has at least one of the following diagnosed conditions: depression, anxiety disorder, bipolar disorder, or schizophrenia.

All regressions used multi-level modeling at the state and facility levels.

## **CHAPTER 5: SUMMARY AND CONCLUSIONS**



## **Key findings**

The dissertation findings' overarching theme is that prescription analgesics are not used frequently enough in a substantial proportion of elderly nursing home residents, while long-acting opioids are inappropriately initiated and used in a large number of other residents. The first aim identified the nursing home's failure to use analgesics when these therapies appeared medically necessary for residents with the most serious, lasting pain (i.e., persistent pain). The second and third aims identified the inappropriate prescribing of long-acting opioids in nursing homes, based on whether the resident had persistent pain, a prior opioid (for transdermal fentanyl initiation), or CNS drug co-prescribing (for oxycodone ER initiation and use).

### Summary of Chapter 2 findings

In Chapter 2 we identified the prevalence of no analgesic prescribing for nursing home residents with persistent pain. We found that 16.7% of residents in our study did not receive any prescription analgesics (i.e., opioid, NSAID, and/or acetaminophen). This prevalence figure for no analgesic prescribing is troubling, because these residents had the most intense pain over a long time period (i.e., daily moderate-to-severe pain for at least three months). We also found that few residents with persistent pain received physical therapy (less than 10% after excluding those without MDS measurements), suggesting these residents did not receive alternative pain treatments.

In Chapter 2 we also identified individual characteristics independently associated with no analgesic prescribing, including increasing age, greater cognitive impairment, being Black or Asian, paying for nursing home expenses without assistance ("self-pay"),

and being a high school or college graduate. This effect increased steadily with increasing age and cognitive impairment. The oldest-old ( $\geq 95$  years) or those with moderate-severe cognitive impairment had the greatest odds for no prescribing (approximately double, compared to those 65-74 or cognitively intact, respectively). These associations for increasing age, greater cognitive impairment, and non-white race support our hypothesis that residents with these characteristics would be less likely to receive analgesic prescriptions for persistent pain. These conclusions raise important concerns about pain treatment disparities for more vulnerable nursing home subpopulations.

Our finding that residents with greater socioeconomic status (i.e. resident self-pay and college/graduate school education) also have greater odds for not receiving prescription analgesics is the opposite conclusion from our hypothesis. This finding may indicate that Medicaid and other government programs to assist residents with nursing home charges also help ensure better prescribing practices, even though Medicare Part D covers residents on Medicaid. This finding that higher SES status may be associated with worse prescribing practices must be explored further.

For facility characteristics, consistent with our hypothesis, we found the increasing proportion of self-pay residents (in the 10-30% and 30-50% categories) and staff hours per resident (peaking at the 3.5-4.0 hour category) were statistically significantly associated with lesser odds for no analgesic prescribing (i.e., equivalent to a greater odds for prescribing. Despite our hypothesis, we did not find any statistically significant association between for-profit status and analgesic prescribing.

Finally, although treated as a confounder in our model, we found that an increase in a resident's number of mood indicators was statistically significantly associated with lower odds (nearly half for the category with most mood indicators) for no analgesic prescribing (i.e., equivalent to greater odds for analgesic prescribing). This may indicate that residents with greater mood distress (e.g., verbal expression of distress, crying, tearfulness, repetitive health complaints) are more likely to receive staff attention for pain medicine prescribing, compared to those residents with less visible distress.

### Summary of Chapter 3 findings

In Chapter 3 we identified the high prevalence of nursing home non-adherence to FDA warnings for transdermal fentanyl use. We found that only 8.2% of residents initiating transdermal fentanyl had persistent pain (i.e. daily moderate-to-severe pain for at least 3 months). This low prevalence for persistent pain raises important concerns that transdermal fentanyl prescribing is not following FDA-approved labeling, which emphasizes that the drug should only be initiated in patients with moderate-to-severe continuous pain (i.e., persistent pain under our definition).<sup>1</sup> Our finding in the sensitivity analysis that at least 30% of residents did not have any pain within 10 days prior to initiating the transdermal fentanyl reinforces this concern.

Our study also found that 36.3% of residents initiating transdermal fentanyl did not receive any opioid prescription in the two-month period prior to initiation, which means they were opioid-naïve. Our study results are concerning, because the FDA has warned repeatedly that transdermal fentanyl should only be initiated in patients who are opioid-tolerant, so prescribing in opioid-naïve residents would clearly be inappropriate.<sup>1</sup>

Furthermore, 20% of the opioid-naïve initiators received transdermal fentanyl at higher doses ( $\geq 50$  mcg/hr), in contrast to precautions in the drug labeling and practice guidelines that opioids should be initiated at lower doses and then titrated upward if necessary.<sup>1-3</sup>

In Chapter 3 we also identified important factors independently associated with opioid-naïve initiation of transdermal fentanyl in nursing homes, including increasing age, greater cognitive impairment, and being Asian. These effects increased steadily with increasing age and cognitive impairment, with the strongest effect for oldest age and greatest cognitive impairment. These associations for increasing age, greater cognitive impairment, and non-white race support our hypothesis that residents with these factors would be more likely to initiate transdermal fentanyl without having a prior opioid prescription. These results raise important concerns about disparities in appropriate treatment for more vulnerable subpopulations within nursing homes. Based on the findings described in Chapters 2 and 3, it is possible that prescription opioids are underprescribed in some circumstances for residents with persistent pain but inappropriately prescribed for residents without such pain.

Our finding that residents with higher SES (self-pay status and more education) had greater odds for opioid-naïve initiation is counter to our hypothesis that higher SES would correspond with better care and more appropriate fentanyl prescribing (i.e., lower odds for opioid-naïve prescribing). This conclusion is similar to our unexpected finding in Chapter 2 that higher SES is associated with worse care (i.e., no analgesic prescribing for pain). This counterintuitive finding, and any possible reasons, must be explored further.

Finally, we did not find that facility characteristics were associated with opioid-naïve initiation, except greater average hours per resident (in the 2.5-3.0 hours category) and proportion of self-pay residents (in the 10-30% and 30-50% categories) were statistically significantly associated with lower odds for opioid-naïve prescribing, which was consistent with our hypothesis for better care (i.e., lower odds for opioid-naïve prescribing) in these facilities.

#### Summary of Chapter 4 findings

In Chapter 4 we identified the high prevalence of nursing home non-adherence to FDA warnings for oxycodone ER use, which was similar to our finding in Chapter 3 for transdermal fentanyl. We found that only 12.0% of residents initiating oxycodone ER had persistent pain under our definition. Most troubling, 28.5% had no pain at their last assessment before initiation. Even for those residents with an MDS assessment 5 days or less before drug initiation, over 20% had no pain. These findings indicate that oxycodone ER prescribing for many residents did not follow the FDA's approved labeling condition that the drug only be used for moderate-to-severe, continuous pain.

We also found that 27% of oxycodone ER initiators were co-prescribed at least one CNS depressant, and 4% were co-prescribed at least two CNS depressants. These study results raise questions about the propriety of this prescribing, because the FDA-approved labeling cautions against the co-prescribing of CNS depressants, particularly in the elderly.<sup>4</sup> Hypnotics, antiemetics, and muscle relaxants were the most frequently co-prescribed with oxycodone ER, which on their own can pose safety risks to elderly patients, including from sedation, respiratory depression, and other adverse effects.<sup>5-7,8</sup>

In particular, we found that sedatives were one of the least prescribed drug categories, except for buspirone, and there were almost no prescriptions for first generation antipsychotics or benzodiazepines. These low prescribing levels for benzodiazepines are probably caused by CMS policies excluding benzodiazepines from the Part D program,<sup>8</sup> rather than FDA regulatory steps. For 92% of residents co-prescribed a CNS depressant, the oxycodone ER drug was prescribed in the lowest dose range ( $\leq 20$  mg), which at least followed FDA precautions that oxycodone ER drugs should be initiated at lower doses in patients who also receive a CNS depressant.<sup>4</sup>

Our alternate analysis reinforces the concerns with CNS drug co-prescribing, because we found that nearly 40% of oxycodone ER initiators were co-prescribed at least 2 CNS agents and 10% were co-prescribed at least 3 CNS agents. This high prevalence of CNS agent co-prescribing with oxycodone ER raises important concerns for potential adverse events, even at lower oxycodone ER doses.<sup>9,10</sup> Drug combinations with opioids, antipsychotics, anti-convulsants, and antidepressants (all co-prescribed in 5% of residents) are particularly dangerous.<sup>11-14</sup> Our finding that 80% of nursing home residents initiating oxycodone ER were co-prescribed at least 9 drugs, and 3.4% of residents were co-prescribed at least 29 drugs, illuminates a very troubling polypharmacy practice for nursing home residents initiating oxycodone ER.

In Chapter 4 we also identified important factors that were independently associated with lower odds for CNS depressant co-prescribing, including increasing age, cognitive impairment, and Black race. This finding contradicted our hypothesis of an opposite effect and suggests that nursing homes may be following more closely the FDA warning against CNS depressant co-prescribing for older, more cognitively impaired, and

Black residents. Our alternate analysis with broader CNS agent categories also found that increasing age had statistically significantly lower odds for CNS agent co-prescribing. In addition, the analysis found that increasing cognitive impairment had higher odds for this co-prescribing, which is opposite the main model finding but consistent with our hypothesis. These results may mean that residents initiating oxycodone ER with greater cognitive impairment are more likely to receive antidepressants, atypical antipsychotics, and/or mood stabilizers, but less likely to receive CNS depressants.

Finally, we found that increasing MDS mood scale scores (treated as a confounder) were associated with higher odds for co-prescribing with 3 or more CNS agents. Most alarming, the highest MDS mood scale score, corresponding with the greatest degree of mood disturbances and agitation, had nearly 4 times the odds for CNS agent co-prescribing. This association is independent of the resident's diagnosis for certain psychiatric conditions which were included in the model. This finding raises important concerns that mood disturbance behaviors (independent of a psychiatric diagnosis) may be a factor in the co-prescribing of 3 or more CNS agents with oxycodone ER initiation. Our study's finding about mood disturbance and CNS agent co-prescribing should be investigated further.

## **Implications and future steps**

The dissertation attempts to provide a foundation for future research assessing nursing home pain management and analgesic prescribing, as well as policies and guidelines in these areas.

### Research implications

Based on the dissertation findings, there are four general areas for further research. First, additional studies should examine some of the assumptions that underlie our findings, particularly the persistent pain definition, appropriateness of analgesics for persistent pain, and these drugs' safety and effectiveness in nursing home residents. Second, further research should examine the heterogeneity in outcomes between residents, facilities, and states, as well as focus on specific subpopulations, rather than relying on average effect estimates to characterize the nursing home population. Third, studies must examine the associations that we identified for inadequate pain management and prescribing practices, including in more recent nursing home populations, and determine if our dissertation findings are replicable. Fourth, further research must be conducted in nursing homes to elucidate the causes for the prescribing patterns and associations that we found, particularly to understand more clearly the underlying mechanisms for inadequate care and health disparities that we identified.

The dissertation's persistent pain definition is the crux for all three aims, but the validity and reliability of this definition for measuring persistent pain must be explored further. Although the MDS 2.0 has been found valid in measuring the pain intensity and duration over the past week,<sup>15</sup> a critical question is the extent of each resident's pain



experience between measurements, which can be up to 90 days between quarterly reports. So a limitation in our definition involves the potential gaps in pain measurement between quarterly MDS assessments. Residents could have many variations in pain intensity and duration during these gaps, including no pain, that could require different care approaches. Studies that measure resident pain directly in nursing homes on a more frequent basis between MDS assessments, using comprehensive and valid methods,<sup>16</sup> could compare these results to persistent pain measurement using our definition. Studies in more recent nursing home populations could also use the revised MDS 3.0 version, which would be more relevant for current practice.<sup>17</sup>

Even if other studies confirm that our reliance on the MDS accurately and reliably measures the most severe, ongoing pain in residents, the question remains whether each of these residents should receive prescription analgesic therapy. Additional study will be necessary to determine those factors in residents with persistent pain that support prescription analgesic use. This research could allow for a more nuanced approach in assessing inadequate analgesic prescribing and identifying those residents who are being neglected. We examined physical therapy and other drugs with possible uses for pain (such as gabapentin for neuropathic pain), but there are many other approaches that nursing homes could use that are not captured in our data, including OTC drugs and social support.<sup>18</sup> Researchers must examine more closely the various treatments for residents with persistent pain in nursing homes, including those not captured in the MDS, to develop a clearer picture for which residents with persistent pain should receive prescription analgesics.

Underlying the concerns we have raised with inadequate nursing home prescribing, particularly for our first aim, lies the fundamental question of each drug's comparative safety and efficacy. Further research will be necessary to compare prescription opioids against each other, as well as prescription opioids to prescription NSAIDs and no prescription analgesics.<sup>19,20</sup> These studies could use essential outcomes, such as cognitive and physical functioning and pain levels for everyday activities, to assess the drugs' effects on residents' quality of life.<sup>19</sup> Studies that measured these outcomes more directly and compared different alternative therapies not measured in the MDS, such as OTC drugs, would be quite useful.<sup>21</sup> Randomized clinical trials for these assessments, where ethically feasible, will be critical.<sup>22</sup>

Additional research must also explore heterogeneity between nursing home residents in their pain experience and factors for care. For example, pain has many different possible causes that can shape the effect on each individual and require different therapeutic approaches.<sup>23</sup> Residents can differ substantially in their pain experiences, as well as factors for their care.<sup>24,25</sup> The estimates from our models are for population average effects, which may not apply to certain subpopulations, such as for persistent pain prevalence and inadequate prescribing. We examined some subgroups in our research, where possible, and found results similar to the general population (e.g., for residents with diabetes), but additional studies should examine more closely residents with specific types of health conditions and pain experiences. Population-average effects can hide important variation within nursing homes for resident care.<sup>25</sup> It would be helpful to understand the extent that individual nursing homes are providing disparate care to residents within their own facilities.

It will also be important to explore variations in our measurements between facilities and regions. For example, studies have shown that clinical practice can vary, depending on the facility and region, in pain management practices, including opioid prescribing.<sup>26,27</sup> These cultural norms can influence strongly the care decisions that are made in institutional settings for treating pain.<sup>21,28</sup> It will be important to assess the variations by region and nursing homes in our outcomes – the prevalence of persistent pain, analgesic prescribing, and non-adherent opioid prescribing. The analysis could also examine the variation between nursing homes and states in resident composition and health indicators, particularly those characteristics included in our models. This assessment could help identify cultural or regional influences on our findings and shape more refined policy approaches.

Our health disparity findings will also require further research for confirmation. It would be helpful to use models with different measures for our facility characteristics and potential confounders. The role of facility quality is critical for our research, including its association with our individual and facility characteristics (such as percentage of self-pay residents) and outcomes (i.e., prescribing for persistent pain and adherence to long-acting opioid guidelines and drug labeling).<sup>25,29</sup> This classic confounding threat must be controlled with more refined measures. Our use of a binary variable to capture a facility's compliance with federal law may have been too blunt, so alternative approaches to measure this concept must be explored. Likewise, a resident's family support can influence care outcomes in our models and could be associated with our examined individual and facility factors.<sup>30,31</sup> However, the binary variable for care meeting participation may lack sufficient refinement to discriminate the degrees of

support. In addition, our models only included variables for mood and ADL assistance as possible additional confounders. Additional research could help refine these models and ensure variables are capturing underlying characteristics that might otherwise bias the results.

In addition to confirming our findings for inadequate pain treatment (Chapter 2), inappropriate opioid prescribing (Chapter 3 and 4), and health disparities related to these outcomes (Chapters 2-4), further research must also explore the underlying mechanisms for these nursing home practices. For example, we must understand further how older age, greater cognitive impairment, and minority race can be associated with underuse of prescription analgesics for persistent pain (Chapter 2) but also overuse for these subpopulations without serious pain (Chapter 3). The mechanisms for such disparities are complex and can be grounded in implicit stereotyping and bias on the part of healthcare providers.<sup>32,33</sup> Qualitative research in nursing homes to explore these mechanisms further will also be crucial.<sup>34</sup>

We must also understand further the influence of government programs, particularly Medicare and Medicaid, on care and prescribing decisions for nursing home residents. For example, the CMS policy to exclude benzodiazepines from Part D coverage essentially halted this drug prescribing in nursing homes, at least for those residents in the Part D program (estimated at more than 80% upon program initiation).<sup>8,35</sup> This financial condition potentially had greater impact on prescribing than any FDA warning or CMS nursing home inspection. Medicaid coverage for nursing home care might also impact pain management decisions.<sup>36</sup> It would be helpful for research to

incorporate these policies more explicitly in analyses for nursing home pain management and analgesic prescribing.

### Policy implications

The dissertation research could also help inform policies and practices to ensure better pain management and analgesic prescribing in nursing homes. These policies and practices could incorporate in particular our findings in Chapters 3 and 4 for long-acting opioid misuse.

As the federal agency charged with ensuring that prescription drugs are safe and effective for their approved uses, FDA must consider steps to protect nursing home residents from dangerous prescribing for long-acting opioids, particularly in residents who do not have any pain, are opioid-naïve (for transdermal fentanyl), or are co-prescribed CNS depressants (for oxycodone ER). Before the time period for our study (2007-2008), FDA took regulatory steps to ensure the safer use of long-acting opioids, such as communications to health care professionals and the public, as well as stronger warnings in drug labeling.<sup>37-43</sup> The high prevalence of non-adherence in nursing homes, though, is extremely concerning, particularly for those residents without any measured pain (i.e., over 30% for transdermal fentanyl and 20% for oxycodone ER in our sensitivity analyses) and who were opioid-naïve (over one-third of transdermal fentanyl initiators).

FDA must take additional action, tailored for the nursing home setting, to address non-adherence to critical conditions for safe opioid use. FDA has recently requested that research be conducted using post-marketing data sources for prescription drug use in

patients to enhance the agency's understanding of actual prescribing practices and dangers.<sup>44</sup> Our dissertation research contributes to this effort. FDA can move forward now based on our research, because these non-adherence findings are not limited by the measurement and methodological challenges we faced in our other models to identify and quantify persistent pain and health care disparities. FDA has regulatory authority directly over the drug manufacturers to require certain steps, particularly through REMS, while FDA can use risk communications and guidance to influence nursing home practices.<sup>45</sup>

First, FDA can update the REMS plan for long-acting opioids to include steps for health care practitioners in nursing homes. The current REMS plan requires that drug manufacturers make training available to health care providers about safe use for long-acting opioids.<sup>46</sup> FDA has developed a blueprint for this training, which covers opioid abuse and misuse risks for the general population.<sup>47</sup> The REMS plan, though, could add specific education for nursing home practitioners about the particular dangers to residents from inappropriate long-acting opioid prescribing. In addition to the widespread use in residents without pain, this training could address the problem of opioid-naïve transdermal fentanyl initiation and CNS drug co-prescribing with oxycodone ER. The REMS plan could also require certifications,<sup>48</sup> based on completed training and written agreements, for health care practitioners in nursing homes to receive the drugs from manufacturers. Finally, FDA could require drug manufacturers to assess the REMS plan effectiveness in nursing homes and submit periodic reports to FDA.<sup>48</sup> It is critical that FDA make these assessments publically available.<sup>48</sup>

Second, FDA could direct specific communications and guidance to nursing homes to address the risks we have identified in this dissertation. Research has indicated

that these risk communications are more effective in changing prescriber behavior when they are more specific, repeated frequently, and acceptable alternatives are available.<sup>49</sup> Although FDA does not exercise regulatory authority over nursing home practices, the agency has issued guidance in the past to assist nursing homes with the safe use of FDA-regulated products, such as medical oxygen.<sup>50</sup> Similarly, FDA could issue guidance to nursing homes based on our research about the dangers of prescribing long-acting opioids to residents who do not have persistent pain, who are opioid-naïve (particularly for transdermal fentanyl), or who are co-prescribed CNS depressants (particularly for oxycodone ER).

CMS is another important federal agency that can implement policies to address these research findings. CMS has regulatory authority over nearly all nursing homes through its Medicare and Medicaid programs. CMS has general regulations prohibiting nursing homes from using “unnecessary drugs” in residents, but these regulations do not provide specific examples or details.<sup>51</sup> The agency has issued recommendations in guidance for appropriate pain management and analgesic use, including that health care practitioners in nursing homes follow FDA-approved labeling conditions for drug prescribing.<sup>52</sup> States are responsible for conducting nursing home inspections and use these recommendations as a guide for inspectional observations.<sup>52</sup> These recommendations, though, do not specifically address the problems identified in this dissertation, including long-acting opioid prescribing in residents without pain, transdermal fentanyl initiation in opioid-naïve individuals, and CNS drug co-prescribing with oxycodone ER.

CMS could issue more detailed recommendations against these practices, along with alternative therapies, that could be tracked in individual inspections. This more specific approach might help to change nursing home practices. In addition, our finding in Chapter 4 that residents initiating oxycodone ER with severe mood disturbances are four times more likely to experience CNS agent co-prescribing may indicate that nursing homes are overmedicating residents with these drugs to quell their mood disturbances, despite earlier CMS guidance against this practice.<sup>52</sup> So CMS should investigate this possibility further.

The Drug Enforcement Agency (DEA) is another federal agency that might contribute to these policy efforts in nursing homes. DEA has regulatory authority over the sale and prescribing of controlled substances, including opioid drugs. Our finding that at least 30-40 percent of transdermal fentanyl and oxycodone ER initiators do not have any pain at their last MDS assessment raises important concerns that the drugs are not actually being administered to these residents. Instead, drug diversion by staff remains a very real concern and must be considered further.<sup>53</sup> DEA has been working with CMS to combat opioid diversion in the Medicaid program.<sup>54</sup> These agencies could investigate more closely the possibility of long-acting opioid diversion in the nursing home context.

Geriatric health organizations are another relevant stakeholder to improve nursing home pain management and analgesic prescribing practices. As described in Chapter 1, the American Geriatric Society (AGS) has issued practice guidelines for the use of analgesics, including opioids, in elderly adults with persistent pain.<sup>2</sup> These recommendations follow the WHO stepped approach for cancer in treating persistent pain



with analgesics. However, the guidelines are very general and fail to address specifically the inadequate pain management and inappropriate prescribing that we identified in our study. At the very least, these guidelines could incorporate recommendations for long-acting opioids, such as clearer precautions against opioid-naïve use, CNS depressant co-prescribing, and prescribing in residents without pain. The American Medical Directors Association (AMDA) has also issued guidelines for pain management in nursing homes, but this guidance is less specific than the AGS guidelines.<sup>3</sup> As the primary organization for nursing homes, it is critical that AMDA provide specific recommendations and advice to nursing homes about these problems with long-acting opioid misuse.

Finally, nursing homes themselves are at the heart of any practice reforms. An important focus in recent years has been on resident-directed care (also known as “culture change”), which attempts to empower nursing home residents with more involvement in decisions about their care.<sup>25</sup> The newer MDS 3.0 assessment tool includes items about a resident’s quality of life. Despite these efforts’ good intentions, nursing homes today face an overwhelming number of responsibilities beyond the core care functions for residents, which are even more burdensome in light of significant resource and staff restraints. There are numerous overlapping regulatory and reform initiatives for nursing homes to track and assess quality indicators.<sup>25</sup> Some have argued that too much focus is placed on indicator tracking and process, rather than essential quality improvements for nursing home residents.<sup>25</sup> And it remains unclear if these efforts have improved quality outcomes.<sup>25</sup>

Given these constraints, we recommend that nursing homes focus first on the problems we identified for long-acting opioid use. Nursing homes can take steps to

ensure that residents without recorded pain in the MDS are not initiated on a long-acting opioid. Nursing homes could also use available approaches to limit polypharmacy in residents,<sup>55</sup> particularly those taking long-acting opioids and CNS agents, and implement checks on transdermal fentanyl prescribing in opioid-naïve residents. These would be specific and manageable actions that could yield tangible and more immediate improvements in resident outcomes.

For longer term approaches to the deeper care issues for pain management and analgesic prescribing, it will be necessary for all stakeholders - researchers, government agencies, practice organizations, nursing homes, practitioners, and residents and their families - to work together in developing, assessing, and acting on the evidence for lasting improvements in nursing home care.

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<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051257.htm>. Accessed April 14, 2015.
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45. Fain K, Alexander GC. Are Food and Drug Administration prescription drug safety plans working? A case study of isotretinoin. *Pharmacoepidemiology and Drug Safety*. Dec 2013;22(12):1258-1262.
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<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>. Accessed April 10, 2015.

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48. Fain K, Nachman KM, Rutkow L. An analysis of FDA's drug safety authorities: challenges and opportunities under a new regulatory framework. *New York University Journal of Legislation and Public Policy*. 2014;17(1):1-36.
49. Dusetzina SB, Higashi AS, Dorsey R, et al. Impact of FDA drug risk communications on health care utilization and health behaviors. *Medical Care*. 2012;50(6):466-478.
50. U.S. Food and Drug Administration. Guidance for Hospitals, Nursing Homes, and Other Health Care Facilities. 2001; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070285.pdf>. Accessed April 14, 2015.
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54. U.S. Centers for Medicare and Medicaid. Drug Diversion in the Medicaid Program. 2012; <http://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/MedicaidIntegrityProgram/Downloads/drugdiversion.pdf>. Accessed April 14, 2015.
55. Garcia-Gollarte F, Baleriola-Julvez J, Ferrero-Lopez I, Cuenllas-Diaz A, Cruz-Jentoft AJ. An educational intervention on drug use in nursing homes improves health outcomes resource utilization and reduces inappropriate drug prescription. *Journal of the American Medical Directors Association*. 2014;15(12):885-891.

# KEVIN M FAIN

## Home Address

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#726  
Washington, DC 20008  
Home (202) 244-6981  
[kevinfain@yahoo.com](mailto:kevinfain@yahoo.com)

## Business Address

Johns Hopkins Bloomberg School  
of Public Health  
Department of Epidemiology  
615 N. Wolfe Street, W6508  
Baltimore, MD 21205  
301-775-1260  
[kfain1@jhu.edu](mailto:kfain1@jhu.edu)

## EDUCATION AND TRAINING

- Expected June 2015    **Doctor of Public Health (DrPH)** in Epidemiology  
Johns Hopkins Bloomberg School of Public Health,  
Baltimore, MD
- Dissertation Proposal: “Assessing the Appropriateness of Opioid  
Prescribing in Elderly Nursing Home Residents”
- Dec 2014    **Certificate in Pharmacoepidemiology and Drug Safety**  
Johns Hopkins Bloomberg School of Public Health,  
Baltimore, MD
- 2014–Current    **Certified in Public Health (CPH)**
- May 2011    **Master of Public Health**  
Johns Hopkins Bloomberg School of Public Health,  
Baltimore, MD  
**Capstone:** FDA’s Implementation of Risk Evaluation and  
Management Strategies for Prescription Drugs: A Three-Year  
Review
- May 2011    **Certificate in Risk Sciences and Public Policy**  
Johns Hopkins Bloomberg School of Public Health,  
Baltimore, MD
- 1994–Current    **Law License**, State Bar of Georgia
- June 1994    **Juris Doctor**  
The University of Chicago Law School, Chicago, IL
- December 1990    **Bachelor of Arts** in History  
Duke University, Durham, NC



## PROFESSIONAL EXPERIENCE

- June 2014-Current     **Center Scholar**, The Center of Excellence in Regulatory Science, Johns Hopkins University, Baltimore, MD  
Evaluate effect of FDA regulatory standards on public health outcomes through quantitative analysis, including
- Adherence to FDA conditions and warnings for long-acting prescription opioids, such as transdermal fentanyl
- Sept 2012-Current     **Center Scholar**, The Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD  
Conduct public health research and advocacy for drug safety, including
- Evaluating FDA's regulation of prescription drug safety through epidemiologic, policy, and legal research, such as Risk Evaluation and Mitigation Strategies (REMS) and post-marketing study commitments
  - Assisting in advocacy and research efforts to ensure greater disclosure by FDA of clinical trial data and post-marketing safety evaluations for prescription drugs
- 2013-2014             **Consultant**, Johns Hopkins Clinic for Public Health Law and Policy, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD  
Assist clinic faculty with class instruction, research, and advocacy for projects involving public health law, including:
- FDA's regulation of caffeine in foods (Fall 2013)
  - FDA's regulation of lethal injection drugs (Spring 2014)
- 2011-2014             **Lerner Fellow and Researcher**, The Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD  
Conduct public health research and advocacy for animal drug and food safety matters, including
- Evaluating FDA scientific risk assessments for animal drug residues in human food, such as hormone drugs
  - Assessing FDA's food safety proposed rules for farms
  - Advocating to Congress and FDA, in correspondence and meetings, for new antibiotic resistance policies
  - Advising on the report "Industrial Food Animal Production in America: Examining the Impact of the Pew Commission's Priority Recommendations" (October 2013)  
<http://www.ncifap.org>

- June-Sept 2013      **Policy/Advocacy Analyst**, Office of Policy and Planning,  
Baltimore City Health Department, Baltimore, MD  
Assisted on health policy projects, including
- Preparing the Community Health Improvement Plan for national accreditation and assisting in plan implementation
  - Researching and preparing a Health Impact Assessment for the Baltimore City Disaster Preparedness and Planning Project
- Jan-Dec 2011      **Independent Consultant**, Washington, D.C.  
Assisted public health organizations with drug safety research and advocacy projects, including
- Reviewing and advising on the Pew Health Group report “After Heparin: Protecting Consumers from the Risks of Substandard and Counterfeit Drugs” (July 2011)  
<http://www.pewtrusts.org/~media/legacy/uploadedfiles/wwwpewtrustsorg/reports/health/PewHeparinFinalHRpdf.pdf>
  - Evaluating and advising on legal and policy issues for the FDA Safety and Innovation Act, particularly for foreign drug safety, supply chain security, and drug manufacturing standards
  - Evaluating and advising on legal and policy issues for the Generating Antibiotic Incentives Now (GAIN) Act
  - Analyzing prescription drug shortage issues and causes
- 2002-2010      **Associate Chief Counsel for Drugs**, Office of Chief Counsel (OCC), U.S. Food and Drug Administration (FDA), Rockville, MD  
Assisted and advised senior FDA officials in numerous legal and policy areas, including
- Drug approval standards and drug safety requirements
  - Regulation of foreign drug manufacturing and imports
  - Current good manufacturing practice (CGMP) standards for drug products
  - Generic and over-the-counter (OTC) drug requirements
  - Counterfeit drug regulation
  - Drug adverse event reporting requirements
  - Prescription drug compounding laws
- Specific responsibilities included
- Reviewing and drafting FDA regulations, guidance documents, warning letters, and citizen petition responses
  - Advising FDA on proposed legislation and FDA’s participation in congressional hearings
  - Assisting FDA on compliance matters and drug litigation

- Supporting FDA officials in interactions with industry, outside counsel, and Congress
- Supervising numerous junior attorneys in these areas

Assisted and advised FDA as a lead attorney in significant initiatives, including

- FDA's ongoing response to the contaminated heparin outbreak of 2008, including subsequent enforcement actions, congressional hearings, and GAO investigations
- FDA's work on legislation to ensure foreign drug supply safety, such as the proposed "Food and Drug Administration Globalization Act of 2009"
- FDA's evaluation of fluoroquinolone drug safety, including its 2008 written response to citizen petition requests and litigation seeking more drug warnings
- FDA's initiative to update the susceptibility test interpretive criteria for antibacterial drugs, including the 2009 guidance for recommended procedures
- FDA's 2007 proposed rule and later rulemaking for new testing and labeling standards for OTC sunscreen drugs
- FDA's initiative to modernize the CGMP regulations, including the 2008 revisions
- FDA's counterterrorism initiatives, including Emergency Use Authorizations

2003-05; 2009-10

**Team Leader**, Drugs Counseling Team, OCC  
US Food and Drug Administration, Rockville, MD  
Management responsibilities for team's eighteen attorneys, including

- Assigning projects to team members
- Working with FDA and OCC management in tracking and coordinating team's projects
- Resolving administrative and legal issues for team

2002-2004

**Recruitment Committee Member**, OCC  
US Food and Drug Administration, Rockville, MD  
Voting member of recruitment committee and assisted in

- Evaluating applicants and planning on-campus interview programs from 2002-2004
- Developing and running the OCC summer legal internship program in 2002 and 2003

Jan-August 2000

**Detail**, Centers for Disease Control and Surveillance (CDC)  
Office of General Counsel, Atlanta, Georgia  
Assisted the Office of General Counsel, CDC, with

- Legal issues for vaccines and laboratory testing

- Emergency preparedness legal issues (e.g., quarantine)
- CDC's Public Health Law Program development
- Successful negotiations with companies to allow National Institute for Occupational Safety and Health (NIOSH) inspections for health hazard evaluations, such as chemical AMT for occupational asthma  
<http://www.cdc.gov/niosh/hhe/reports/pdfs/2000-0096-2876.pdf>

1998-2002

**Associate Chief Counsel for Enforcement, OCC**

US Food and Drug Administration, Rockville, MD

Represented FDA with Department of Justice (DOJ) in federal enforcement and defensive litigation throughout the United States, with duties including

- Successfully representing FDA in enforcement actions against food and drug manufacturers violating FDA law
- Successfully defending FDA in lawsuits brought by generic drug manufacturers challenging innovator drug exclusivity, such as Watson Pharmaceuticals, Inc. v. Henney, 194 F.Supp.2d 442 (D.Md. 2001); Mylan Pharmaceuticals, Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001); and Andrx Pharmaceuticals, Inc. v. Biovail Corporation, 276 F.3d 1368 (Fed. Cir. 2002)
- Drafting pleadings and motions; handling settlement negotiations; and participating in court arguments
- Assisting DOJ, including Office of Solicitor General, in appeals of cases
- Supervising FDA attorneys handling litigation

1995-1998

**Associate Chief Counsel for Veterinary Medicine, OCC**

Advised and assisted FDA officials on animal drug legal issues, including

- Animal drug approvals, manufacturing and labeling
- Debarment and disqualification of individuals in the animal drug industry

1994-95

**Law Clerk, Honorable John F. Nangle**

U.S. District Judge, Savannah, GA

Assisted federal judge in handling of court cases, including drafting judicial opinions.

**PROFESSIONAL ACTIVITIES**

2014-Current

Member, Expert Working Group for Medical Countermeasure Emergency Communication Strategies, UPMC Center for Health Security, Baltimore, Maryland

2014–2015	Co-President, Johns Hopkins Chapter, International Society of Pharmacoepidemiology (ISPE)
2014	Member, Task Force for Academic Freedom, Johns Hopkins University
2014	Ad-Hoc Member, Hearing Panel for Student Grievances, Johns Hopkins Bloomberg School of Public Health
2013-2014	DrPH Student Evaluation Team for DrPH Executive Board, Johns Hopkins Bloomberg School of Public Health
2013	Surveillance and Outbreak Response Team (SORT), Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
2012-2013	Co-Coordinator, General Epidemiology/Methods Journal Club
2011-Current	Founding Member, Johns Hopkins Chapter, ISPE
2010-2011	Representative, Deans for Students Network, Johns Hopkins Bloomberg School of Public Health

## EDITORIAL ACTIVITIES

2012-Current	Ad Hoc Reviewer: <i>American Journal of Public Health</i> , <i>JAMA</i> , <i>Medical Care</i> and <i>BMC Health Services Research</i> .
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## HONORS AND AWARDS

2014-2015	Center Scholar, Center of Excellence in Regulatory Science (CERSI), Johns Hopkins Bloomberg School of Public Health <a href="http://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/people/cersi-scholars/">http://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/people/cersi-scholars/</a>
2013-2015	Sommer Scholar, Johns Hopkins Bloomberg School of Public Health <a href="http://www.jhsph.edu/admissions/scholarships/institutional-scholarships/sommer-scholars/scholars/">http://www.jhsph.edu/admissions/scholarships/institutional-scholarships/sommer-scholars/scholars/</a>

2012-2015	Center Scholar, The Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health <a href="http://www.jhsph.edu/research/centers-and-institutes/center-for-drug-safety-and-effectiveness/academic-training/center_scholars/index#Fain">http://www.jhsph.edu/research/centers-and-institutes/center-for-drug-safety-and-effectiveness/academic-training/center_scholars/index#Fain</a>
2013	Marilyn Menkes Book Award, Department of Epidemiology
2012-13; 2011-12	Lerner Fellow, The Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health <a href="http://www.jhsph.edu/research/centers-and-institutes/johns-hopkins-center-for-a-livable-future/about/fellows/bios/fain.html">http://www.jhsph.edu/research/centers-and-institutes/johns-hopkins-center-for-a-livable-future/about/fellows/bios/fain.html</a>
2011-2012	Health Resources and Services Administration (HRSA) Public Health Traineeship Grant <a href="http://www.jhsph.edu/offices-and-services/practice-and-training/awards-grants-training/hrsa-trainees/2011.html">http://www.jhsph.edu/offices-and-services/practice-and-training/awards-grants-training/hrsa-trainees/2011.html</a>
2008	FDA Award of Merit (Highest FDA Award)
2007, 2001	FDA Commissioner's Special Recognition Award (Group)
2002	FDA's Outstanding Service Award for Litigation
1992	Chicago Law Foundation Grant for Legal Aid Service
1987-1990	Magna Cum Laude, Duke University

## PUBLICATIONS

### Original Research

2015	<b>Fain KM</b> , Rosenberg PB, Pirard S, Bogunovic O, Spira AP. Markers of impaired decision making in nursing home residents: assessment by nursing home staff in a population based study. Journal of the American Medical Directors Association. In Press. February 14, 2015. DOI: <a href="http://dx.doi.org/10.1016/j.jamda.2015.01.080">http://dx.doi.org/10.1016/j.jamda.2015.01.080</a>
2014	<b>Fain KM</b> , Nachman KE, Rutkow L. An analysis of FDA's drug safety authorities: challenges and opportunities under a new regulatory framework. New York University Journal of Legislation and Public Policy. 2014; 17(1): 1-36.

- 2013 Yu T, **Fain K**, Boyd CM, Singh S, Weiss CO, Li T, Varadhan R, Puhan M. Benefits and harms of roflumilast in moderate to severe COPD. *Thorax*. 2014; 69: 616-622.
- 2013 **Fain K**, Daubresse M, Alexander GC. The Food and Drug Administration Amendments Act and postmarketing commitments. *JAMA*. 2013; 310(2):202-4.

### **Invited Commentaries**

- 2014 **Fain KM** and Alexander GC. Mind the gap: understanding the effects of pharmaceutical direct-to-consumer advertising. *Medical Care*. 2014; 52(4): 291-293.
- 2013 **Fain K** and Alexander GC. Are Food and Drug Administration prescription drug safety plans working? A case-study of isotretinoin. *Pharmacoepidemiology and Drug Safety*. 2013; 22(12): 1258-1262.

### **Letters**

- 2014 **Fain KM** and Alexander GC. Disposing of medicines safely. *American Journal of Public Health*. October 16, 2014: e1–e2. doi:10.2105/AJPH.2014.302296
- 2014 Tsung Y, **Fain K**, Puhan M. Systematic reviews of benefits and harms in clinical trials. *BMJ*. 2014; 348: g3510.
- 2014 **Fain K** and Alexander GC. Reply letter: Are Food and Drug Administration prescription drug safety plans working? A case-study of isotretinoin. *Pharmacoepidemiology and Drug Safety*. 2014; 23(4): 440-441.
- 2013 **Fain K** and Alexander GC. Drug Postmarketing Studies – Reply. *JAMA*. 2013; 310(22): 2459-2460.

### **Other**

- 2014 “Do stricter controls curb opioid abuse?” The Conversation. Daubresse M, **Fain KM**, Alexander GC. November 14, 2014.  
<http://theconversation.com/do-stricter-controls-curb-opioid-abuse-32788>

- 2014 “State Department of Corrections are Violating FDA’s Investigational New Drug Regulations By Experimenting with Lethal Injection Drugs.” Johns Hopkins Clinic for Public Health Law and Policy. Miller JD, Davis A, **Fain K**, Wolfson JA, Rosen J, Teret S. May 5, 2014.
- <http://www.jhsph.edu/research/centers-and-institutes/center-for-law-and-the-publics-health/Lethal%20Injection%20Policy%20Paper%20Final.pdf>
- 2013 “Comments on the Proposed Rule for Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption and the Proposed Rule for Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food.” The Center for a Livable Future, Johns Hopkins Bloomberg School of Public Health. **Fain KM**, Lawrence R, Nachman KE, Martin RP, Klein RA, Smith TJ. November 15, 2013.
- <http://www.livablefutureblog.com/2013/11/how-fda-should-regulate-the-safety-of-fruits-and-vegetables>
- 2007 Fain K and Sobel J, "Control of Foodborne Diseases," Chapter 14, *Law in Public Health Practice* (Oxford University Press 2003, Second Edition 2007)

## TEACHING

### Guest Lectures

*Food and Drug Law Institute. Washington, DC.*

“The New Drug Approval Process: New Drug Research and Development”

“The New Drug Approval Process: NDA Submission and Review”

Introduction to Drug Law and Regulation.

May 28, 2015

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Health Policy and Management.*

“FDA and the Law”

Public Health and the Law.

February 17, 2015.



“The Public Process for Federal Agency Policy and Rulemaking”  
Public Health Agencies: Law, Policy, and Practice.  
April 3, 2013; April 2, 2014; April 1, 2015.

“Legal and Policy Background for Risk Management”  
Risk Policy, Management, and Communication.  
November 19, 2012; April 1 and November 7, 2013;  
March 26 and November 3, 2014; March 25, 2015.

“FDA Citizen Petitions: Process and Results”  
Johns Hopkins Clinic for Public Health Law and Policy.  
October 31, 2013.

“Introduction to Congressional Hearings for Risk Policy Issues”  
Risk Policy, Management, and Communication.  
December 3, 2012.

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Epidemiology.*

“Selection of Evidence for Benefit-Harm Assessment”  
Comparative Effectiveness Research: Outcome Measurement.  
July 1, 2014 (with Milo Puhan and Tsung Yu).

“FDA’s Avandia Decision: Lessons Learned in Taking the Middle Road”  
Pharmacoepidemiology.  
June 21, 2013.

“Standards for Evaluating Epidemiologic Evidence: U.S. Food and Drug  
Administration and U.S. Preventive Services Task Force”  
Epidemiology Workshop: Interpreting and Using Epidemiologic Evidence.  
January 18, 2013.

“Evaluating an Epidemiological Study”  
Epidemiology Workshop: Interpreting and Using Epidemiologic Evidence.  
January 15, 2013.

*Temple University, Department of Public Health. Philadelphia, PA.*

“FDA Prescription Drug Regulation”  
Political and Economic Aspects of Health.  
September 25, 2014.

*Johns Hopkins Bloomberg School of Public Health. White Oak, MD.  
Fellows Program for U.S. Food and Drug Administration.*

“Post-Marketing Surveillance: The Continuing Story”  
Topics in Clinical Trials.  
February 28, 2014 (in class); March 23, 2015 (online course)

*American University Washington College of Law. Washington, DC.*

“When Does an Agency Rulemaking Exceed a Grant of Statutory Authority?”  
Health Law Seminar: Legislation and Regulatory Process.  
October 31, 2012 (with William McConagha); November 7, 2013 (on own).

“When Can an Agency Use Enforcement Discretion to Achieve Specific Public Health Goals?”  
Health Law Seminar: Legislation and Regulatory Process.  
November 14, 2014 (with William McConagha).

*Georgia State University College of Law. Atlanta, GA.*

“Control of Foodborne Diseases”  
Public Health Law.  
March 18, 2003 (with Jeremy Sobel).

### **Teaching Assistant**

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Health Policy and Management.*

Risk Policy, Management, and Communication.  
January-March 2012; October-December 2012.

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Epidemiology.*

Professional Epidemiology Methods  
January-March 2015.  
Lead teaching assistant. Led laboratory discussion sessions.

Comparative Effectiveness Research: Outcomes Measurement.  
June 2012; June-July 2014.

Pharmacoepidemiology.  
June 2013.

Epidemiology Workshop: Interpreting and Using Epidemiological Evidence.  
January 2013.  
Led laboratory discussion sessions.

Epidemiology Methods 751 and 752  
August-December 2012.  
Assisted in leading laboratory discussion sessions.

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Biostatistics.*

Statistical Methods in Public Health 624.  
March-May 2012; March-May 2013.

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Master of Public Health Program.*

Master of Public Health Capstones: Epidemiology and Health Policy Topics.  
January-May 2014.

### **Tutoring**

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Epidemiology.*

Epidemiology Methods 751 and 752.  
September-December 2013.

Written Comprehensive Exam.  
May 2013.

*Johns Hopkins Bloomberg School of Public Health. Baltimore, MD.  
Department of Biostatistics.*

Statistical Methods in Public Health 622 and 623.  
October 2011-March 2012.

### **RESEARCH GRANT PARTICIPATION**

January 2012- May 2013	“Prediction of Individual Treatment Outcomes in Patients with Chronic Disease.” (6/1/11-5/31/13) Grant UL1 RR 025005. National Center for Research Resources, National Institutes of Health. Principal Investigator: Milo Pahan. Role: Student Investigator.
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Assisted in conducting epidemiologic research for the safety and effectiveness of roflumilast, including

- Identifying and analyzing FDA review documents assessing the benefits and harms of roflumilast.
- Identifying relevant observational studies to assess background harm rates in relevant populations.

## PRESENTATIONS

- |      |  |
|------|--|
| 2015 | FDA 2015 Office of Regulatory Science & Innovation (ORSI) Science Symposium, April 27, 2015. Silver Spring, MD. Poster Presentation. “Development of Regulatory Approaches to Optimizing Safe Use: the Case of Nursing Home Opioids.” <b>Fain KM</b> , Castillo-Salgado C, and Alexander GC. |
| 2015 | Internal Grant Writing Review Seminar, Department of Health Services, Policy & Practice, Brown University School of Public Health. April 15, 2015. Providence, Rhode Island. “Inappropriate Fentanyl Prescribing Among Nursing Home Residents in the United States.”                         |
| 2015 | Works-in-Progress Seminar, Center for Gerontology and Healthcare Research, Brown University School of Public Health. April 13, 2015. Providence, Rhode Island. “Frequency and Predictors of Analgesic Prescribing in U.S. Nursing Home Residents with Persistent Pain.”                      |
| 2014 | Opioid Safety and Naloxone Network, National Harm Reduction Conference, October 25, 2014. Baltimore, Maryland. “Regulatory Options for the U.S. Food and Drug Administration to Switch Naloxone Drug Products from Prescription to Over-the-Counter Status.”                                 |
| 2014 | Professional Epidemiology Special Interest Group, Masters of Public Health Program, September 18, 2014. Baltimore, Maryland. “Professional Epidemiology at the U.S. Food and Drug Administration.”   |
| 2014 | Lethal Injection Strategy Session for Litigators, The Lethal Injection Project of the Berkeley Law Death Penalty Clinic. Sidley Austin, L.L.P. April 24, 2014. Chicago, Illinois. “FDA Framework for Lethal Injection Drugs.”  |

- 2014 Pharmaceutical Health Services Research Seminar, University of Maryland Baltimore School of Pharmacy, April 21, 2014. Baltimore, Maryland. “FDA’s Implementation of Risk Evaluation and Mitigation Strategies (REMS): An Analysis of the First Four Years.”
- 2012 Doctor of Public Health Seminar, Johns Hopkins Bloomberg School of Public Health, November 1, 2012. Baltimore, Maryland. “An FDA and Public Health Perspective for Regulating Prescription Drug Safety.”
- 2012 American Association of Geriatric Psychiatry, Annual Meeting, March 18, 2012. Washington, DC. Poster Presentation. “Depressed Mood in Nursing Home Residents: An Analysis of Data from the 2004 National Nursing Home Survey.” **Fain K**, Bogunovic O, and Pirard S.
- 2012 Partnerships in Clinical Trials, Annual Meeting, March 6, 2012. Orlando, Florida. Roundtable Presentation. “Cultivate the Skill Sets to Understand, Comply with, and Help Refine FDA Pharmacovigilance Regulations.”
- 2011 Pew Health Group, The Pew Charitable Trusts, July 20, 2011. Washington, DC. “FDA Drug REMS Implementation.”
- 2011 Partnerships in Clinical Trials, Annual Meeting, April 1, 2011. Phoenix, Arizona. Panel Presentation. “Implement a Comprehensive Clinical Trial Drug Safety Program and Improve Quality from Clinical Development to Post-Approval.”
- 2010 Anna Baetjer Society Seminar, September 29, 2010. Johns Hopkins Bloomberg School of Public Health. Baltimore, MD. Panel Presentation. “Sharing Experiences in Government and Policy.”
- 2002 Food and Drug Law Institute Educational Conference, April 17, 2002. Washington, DC. Panel Presentation. “In an Era of Refocused GMPs, What’s the Industry to Do?”

## **MEDIA**

- July 2015 “Journal Highlights. Journal of the American Medical Directors Association.” July 2015. Jeffrey S. Eisenberg. Caring for the Ages.

- July 2013 “Kevin Fain DrPH Epidemiology Student.” July 2013. Johns Hopkins Bloomberg School of Public Health Webpage. <http://www.jhsph.edu/news/stories/2013/kevin-fain-drph-epidemiology.html>
- July 2013 “After FDA Approval, Drugmakers Often Miss Study Mark.” July 11, 2013. Jessica Naudziunas. National Public Radio Shots. <http://www.npr.org/blogs/health/2013/07/09/200506488/after-fda-approval-drugmakers-often-miss-study-mark>
- July 2013 “Author Insights: More Companies Following Through on Postmarketing Safety Studies But More Improvement Is Needed.” July 9, 2013. Bridget M. Kuehn. news@JAMA. <http://newsatjama.jama.com/2013/07/09/author-insights-more-companies-following-through-on-postmarketing-safety-studies-but-more-improvement-is-needed/>
- July 2013 “Are Drugmakers Following Through On Post-Marketing Commitments?” July 10, 2013. Ed Silverman. Pharmalot.

#### **ADDITIONAL INFORMATION**

- Skilled in STATA and SAS
- Volunteering with Johns Hopkins Student Outreach Resource Center in Baltimore, Maryland (2011-2013)
- Mandel Legal Aid Clinic at the University of Chicago Law School (1992-1994)