

Original Article

Frequency of Long-Acting Opioid Analgesic Initiation in Opioid-Naïve Nursing Home Residents

David M. Dosa, MD, MPH, David D. Dore, PharmD, PhD, Vincent Mor, PhD, and Joan M. Teno, MD, MS

Center for Gerontology and Health Care Research (D.M.D., V.M., J.M.T.) and Department of Community Health (D.D.D., V.M., J.M.T.), The Warren Alpert Medical School at Brown University; Veterans Administration Medical Center (D.M.D.); and Division of Geriatrics (D.M.D., J.M.T.), Rhode Island Hospital, Providence, Rhode Island; and i3 Drug Safety (D.D.D.), Waltham, Massachusetts, USA

Abstract

A U.S. Food and Drug Administration (FDA) warning against morbidity and death associated with the initiation of transdermal fentanyl in previously opioid-naïve patients has been issued. Additional warnings against opioid-naïve initiation are included in the package inserts for several other long-acting opioids (LAOs). Frail, older nursing home (NH) residents with renal and hepatic insufficiency have increased risk of adverse reactions from initiation of LAOs. Little is known about the frequency of opioid-naïve LAO initiation among NH residents. To ascertain the frequency of LAO initiation among residents residing in Rhode Island NHs, an analysis of 2004–2005 Rhode Island Medicaid pharmacy claims data linked to the Minimum Data Set was conducted. Of the 591 Medicaid residents who initiated therapy with an LAO, 232 (39.3%) were opioid naïve. Furthermore, naïve initiation was more frequent among those with advanced age and those with cognitive impairment. In an exploratory multivariable logistic regression model, opioid-naïve LAO initiation was associated with a diagnosis of Alzheimer's dementia and chewing difficulties. Opioid-naïve residents were also more likely to initiate on fentanyl relative to other LAOs (60.3% vs. 46.4%) and to use higher initial dosages. Given the significance of the FDA warning, including a “black box” warning with transdermal fentanyl, this rate of naïve LAO initiation warrants efforts to further study the prescribing of opioids in NH residents. J Pain Symptom Manage 2009;38:515–521. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Long-acting opioids, nursing home, opioid naïve, pain management, chronic pain, medication error

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Address correspondence to: David Dosa, MD, MPH, Division of Geriatrics, Brown University, Rhode Island Hospital, 593 Eddy Street, APC 424, Providence, RI 02903, USA. E-mail: david_dosa@brown.edu

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Introduction

A U.S. Food and Drug Administration (FDA) public health advisory warning against morbidity and death associated with the initiation of transdermal fentanyl in previously opioid-naïve patients has been issued.¹ Additional warnings against opioid-naïve initiation are included in the package insert for several other long-acting opioids (LAOs), including morphine sulfate controlled release (CR) and oxycodone CR.²⁻⁴ Despite these warnings, little is known about how often LAOs are initiated in drug naïve elderly patients, particularly those who reside in the nursing home (NH).

It is well known that NH residents are at high risk for adverse drug events. NH residents use more medications than patients in other clinical settings.⁵ In part related to the extent of medication exposure, the Institute of Medicine identified NHs as the most common location for medication errors, estimating that 800,000 prescription-related errors occur annually.⁶ In addition to the high frequency of medication use, the majority of NH residents have high levels of baseline frailty including cognitive and functional deficits, and renal/hepatic insufficiency that leave them at high risk for adverse reactions.

Previous research has suggested that opioid medications are associated with a large number of adverse drug events in the NH environment. A study of long stay residents in two academic facilities by Gurwitz et al. noted that errors with opioid medications were frequent, occurring in 51 of 815 total medication adverse events identified over a nine-month period.⁷ The Bergen Nursing Home study noted that opioid analgesics were the most common therapeutic group associated with adverse drug reactions.⁸ A Veterans Administration analysis of NH care units also noted opioids to be the agents most likely to cause adverse events.⁹

Given the recent FDA warnings and the evidence suggesting that the use of opioids has increased markedly over the last 20 years,^{10,11} the purposes of this study were to quantify the prescribing of LAO analgesics to opioid-naïve Medicaid enrollees residing in Rhode Island NHs and to identify correlates of its occurrence.

Methods

Data Sources

The frequency of LAO initiation was quantified among opioid-naïve NH residents using Rhode Island pharmacy claims data from the second quarter of 2004 through calendar year 2005. The validity of Medicaid prescription claims data for identifying medication use has been previously established.^{12,13} Claims data were then linked using enrollee identifiers to NH Minimum Data Set (MDS) (see below) data for calendar years 2004 and 2005 by a third party. Data were then deidentified per federal standards prior to being turned over to study investigators; therefore, the Institutional Review Board at Brown University waived review after being consulted.

Study Sample

Fig. 1 shows the selection criteria for the studied cohort. A total of 11,934 Medicaid supported residents in 72 Rhode Island NHs were identified between the second quarter of 2004 through calendar year 2005. Medicaid claims data were then used to identify new prescriptions for LAOs, including transdermal fentanyl, long-acting oxycodone, or long-acting morphine sulfate. Prescriptions for LAOs were considered to be new if there was evidence of at least one non-LAO medication claim (e.g., antihypertensive, diabetic medication) in the preceding 60 days without evidence of another LAO in the same period. Based on these criteria, a total of 929 residents were identified as new LAO initiators.

Given that hospitals do not bill Medicaid for medications, a total of 84 residents with evidence of hospitalization in the seven days prior to initiating an LAO were excluded. An additional 217 residents were excluded due to incomplete MDS assessments or inconclusive data related to hospitalization. Finally, 37 residents were excluded because there was no MDS assessment available prior to LAO initiation. A total cohort of 591 residents was, therefore, evaluated. An analysis of the excluded residents found that, in general, they were slightly younger and less impaired than the included population, but were otherwise demographically similar.

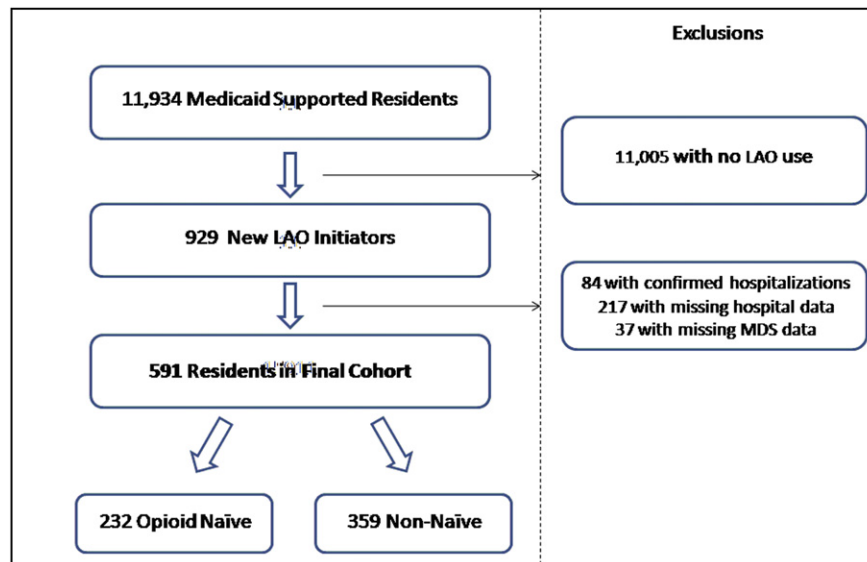


Fig. 1. Cohort selection criteria. LAO = Long-acting opioids including transdermal fentanyl, morphine sulfate controlled release, and oxycodone controlled release; MDS = minimum data set.

Medication Exposure

Residents within the final cohort were then classified as opioid naïve vs. non-opioid naïve at the time of LAO initiation. If there was no evidence of short-acting opioid (SAO) use, regardless of dosage, in the 60 days prior to LAO initiation, the resident was defined as opioid naïve. In Rhode Island, prescriptions for controlled substances, including opioid drugs, must be limited to a 30-day supply. As such, a 60-day look back period was chosen for SAO claims to assess whether the residents were drug naïve.

Preparations of the following medications were considered SAO: hydrocodone, codeine, transbuccal fentanyl, oxycodone, morphine sulfate, propoxyphene, hydromorphone, meperidine, and methadone. Oral, sublingual, injectable, intravenous, and rectal formulations were considered. The pharmacy claims provided information on the dosage-form strength, quantity dispensed, and number of days supplied for each dispensing. For long-acting oral formulations, the average daily dose of each opioid was calculated by dividing the product of the dose per tablet/capsule and the dispensed quantity by the total days of supply dispensed for each prescription claim. An analogous approach was used for estimating the daily dose of fentanyl, accounting for

convention of labeling these products according to amount of drug delivered per hour. For comparability, dosages of opioids were then converted to oral morphine equivalents per 24 hours, regardless of the frequency of dosing, assuming that oral morphine and oral oxycodone are equipotent, that 100 mcg of transdermal fentanyl equals 7.5 mg of oral morphine, and that oral hydromorphone is four times as potent as oral morphine.^{14–16}

Sociodemographic Characteristics and Medical Conditions

Data regarding age, gender, race, insurance status (e.g., self-pay, additional private insurance), do-not-hospitalize orders, do-not-resuscitate orders, hospice care, and education were obtained from the most recent MDS, which is obtained prior to opioid initiation. The MDS is an assessment instrument required in all federally certified NHs and contains standardized demographic and clinical variables collected at quarterly intervals and whenever there is a major change in condition.¹⁷ Information related to medical conditions also was obtained from the MDS, including key diagnoses, functional status, difficulty chewing/swallowing, and cognition. Functional status was determined using the Activities of Daily Living Hierarchy Score (scores

ranging from 0 [full independence] to 6 [total dependence]).¹⁸ Cognition was measured based on the validated cognitive performance scale (scores ranging from 0 [intact] to 6 [very severe impairment]).¹⁹

Statistical Analysis

Demographic and clinical factors described above were assessed using univariate and bivariate analyses comparing the distribution of prespecified factors with the Chi-square test. Furthermore, an exploratory multivariable logistic regression model was used to derive estimates of the adjusted odds ratio (AOR) and 95% confidence intervals (95% CIs) to quantify the association of resident characteristics with naïve LAO initiation. All analyses were performed using SAS Version 9.1 (Cary, NC).

Sensitivity Analysis

A series of sensitivity analyses were conducted to evaluate the impact of the chosen definition of opioid naïvety on the overall results. In one series, the definition of opioid naïvety was changed from 60 days to 30 days. A second sensitivity analysis used 90 days as a definition. In another sensitivity analysis, methadone products were included as an LAO, but were excluded in the final assessment secondary to limited use in the NH cohort. Finally, an analysis was conducted removing the lowest dosage of each long-acting product, including fentanyl 12.5 mcg/h.

Results

Demographics

Overall, a total of 591 residents were identified in the study cohort (Fig. 1). Of the 591 residents, 232 (39.3%) were opioid naïve at the time of LAO initiation. In general, naïve LAO initiation was more frequent among those with advanced age and those with increased cognitive impairment, although these findings were not statistically significant when entered into an exploratory logistic regression (Table 1). Opioid-naïve LAO initiation was associated with a diagnosis of Alzheimer's dementia and the identification of chewing difficulties on the most recent MDS prior to initiation.

Drug Selection and Initial Dosing

Table 2 shows the distribution and mean daily dose in oral morphine equivalents of LAO among opioid-naïve and non-naïve NH residents. In general, opioid-naïve residents were more likely to initiate fentanyl relative to other LAOs (60.3% vs. 46.4%) and to use higher initial dosages of fentanyl in their first prescription (59.7 mg vs. 57.7 mg mean dosage). Non-naïve residents were more likely to initiate LAOs using oxycodone SR (sustained release) (48.5%) vs. fentanyl (46.5%) or SR morphine (5%), and to initiate on lower overall dosages.

Sensitivity Analyses

The results presented in Table 1 were insensitive to changes in the definition of naïvety from 30 to 60 to 90 days. When methadone was included as an LAO, the estimated proportion for residents who were opioid naïve upon initiation changed only slightly from 39.3% to 40.9%. Removing low doses (e.g., oxycodone SR 10 mg) from the analysis attenuated the proportion of naïve initiators slightly to 34.6%.

Discussion

The initiation of long-term opioids in opioid-naïve individuals has been highlighted by the U.S. FDA as a potentially dangerous practice. A "black box" warning exists for the use of transdermal fentanyl in opioid-naïve individuals. Similar warnings exist in the package inserts of other LAOs. Despite these warnings, this study suggests that the practice of using LAOs in opioid-naïve individuals is common, occurring in over one-third of all cases of LAO initiation among Medicaid patients in Rhode Island NHs during a two-year period. It is noteworthy that this study used a very liberal definition of opioid naïvety. Residents were considered non-naïve if there was any evidence of SAO use regardless of the dosage. It is, therefore, likely that the actual rate of inappropriate initiation is somewhat higher than presented.

Among opioid-naïve initiators, the most commonly initiated agent was transdermal fentanyl, the subject of the most stringent warnings from the FDA. Naïve initiators were also more likely to initiate long-acting products at

Table 1
 Characteristics of Opioid-Naïve and Non-Naïve NH Residents Who Initiated a LAO Analgesic

	Naïve Initiators (n = 232) n (%)	Non-Naïve Initiators (n = 359) n (%)	AOR (95% CI) ^a
Demographics			
Age (years)			
<65	21 (9.1)	55 (15.3)	Reference
65–74	24 (10.3)	56 (15.6)	1.1 (0.5–2.4)
75–84	76 (32.8)	111 (30.9)	1.5 (0.8–3.0)
≥85	111 (47.8)	137 (38.2)	1.9 (0.9–3.8)
Women	178 (76.7)	256 (71.3)	1.4 (0.9–2.1)
Non-Hispanic White	209 (90.1)	328 (91.3)	0.8 (0.4–1.5)
Education			
Less than high school	118 (50.9)	201 (55.9)	Reference
High school diploma	73 (31.4)	93 (25.9)	1.4 (0.9–2.2)
At least some college/technical school	41 (17.7)	65 (18.1)	1.5 (0.7–3.0)
Speaks English	203 (87.5)	330 (91.9.0)	0.7 (0.3–1.6)
Do-not-resuscitate order	152 (65.5)	237 (66.0)	0.9 (0.6–1.4)
Do-not-hospitalize order	36 (15.5)	68 (18.9)	0.6 (0.3–1.0)
Hospice care	16 (6.9)	18 (5.0)	1.1 (0.5–2.5)
Functional status			
ADL score^b			
All independent	17 (7.3)	46 (12.8)	Reference
Supervision only/limited at most	40 (17.3)	76 (21.2)	1.5 (0.7–3.1)
Early extensive dependence/mid-to-late extensive dependence	58 (25.0)	101 (28.1)	1.4 (0.6–2.9)
Mid-to-late dependent/all dependent	117 (50.4)	136 (37.9)	1.5 (0.7–3.1)
CPS score^c			
0–1	64 (27.6)	143 (39.8)	Reference
2–4	120 (51.7)	179 (49.9)	1.1 (0.7–1.8)
5–6	48 (20.7)	37 (10.3)	1.4 (0.7–2.8)
Difficulty chewing	73 (31.5)	65 (18.1)	1.7 (1.1–2.7)
Difficulty swallowing	78 (33.6)	81 (22.6)	1.4 (0.9–2.2)
Prior diagnoses			
Congestive heart failure	56 (24.0)	87 (24.2)	1.1 (0.7–1.8)
Arthritis	57 (24.6)	115 (32.0)	0.6 (0.4–1.0)
Hip fracture	16 (6.9)	23 (6.4)	0.9 (0.4–1.9)
Alzheimer's disease	36 (15.5)	23 (6.4)	2.2 (1.1–4.3)
Stroke	36 (15.5)	51 (14.2)	0.9 (0.6–1.6)
COPD	50 (21.6)	83 (23.1)	1.0 (0.6–1.6)
Cancer	25 (10.8)	47 (13.1)	1.0 (0.6–1.8)

CI = confidence interval; ADL = activities of daily living; CPS = cognitive performance scale; COPD = chronic obstructive pulmonary disease.

^aEstimates derived from a multivariable logistic regression model. Estimates adjusted for other variables in the table.

^bADL status based on the MDS ADL scale; measured in the most recent MDS obtained before LAO initiation.

^cCognitive status based on six-point CPS; measured in the most recent MDS obtained before LAO initiation.

higher dosages than non-naïve initiators. Residents with Alzheimer's dementia and those with chewing difficulties were also more likely to be opioid naïve upon LAO initiation. These residents represent a potential high-risk group in terms of the probability for adverse medication events, making future work to determine the morbidity and mortality associated with naïve initiation essential. Furthermore, the recent FDA warnings about morbidity and mortality associated with naïve initiation lend face validity to the importance of these findings.

Finally, these results are noteworthy given the concern for NH-related medication errors emphasized in the U.S. Institute of Medicine Report, "To Err is Human."²⁰ Research to date on adverse drug events in the NH setting has pointed to inappropriate drug selection, dosing, and subsequent monitoring as the most common reasons for medication error. The results of this study suggest potential problems with several of these areas, particularly inappropriate drug selection and dosing. Future work should focus on how opioids are prescribed in the NH and whether adequate

Table 2
Distribution and Mean Daily Dose in Oral Morphine Equivalents of LAO Analgesics Among Opioid-Naïve and Non-Naïve NH Residents^a

	Opioid-Naïve Initiators (n = 232)		Non-Opioid Naïve Initiators (n = 359)	
	% of Total Use n (%)	Mean Dose mg ^b (median)	% of Total Use n (%)	Mean Dose mg ^b (median)
First prescription ^c				
Transdermal fentanyl	140 (60.3)	59.7 (45.0)	167 (46.5)	57.7 (45.0)
Oral morphine	8 (3.4)	36.3 (30.0)	18 (5.0)	60.1 (30.0)
Oral oxycodone	84 (36.2)	34.1 (20.0)	174 (48.5)	33.2 (20.0)
Overall use				
Transdermal fentanyl	88 (37.9)	45.0 (45.0)	104 (29.0)	44.7 (45.0)
Oral morphine	11 (4.7)	58.3 (45.0)	36 (10.0)	75.3 (56.3)
Oral oxycodone	133 (57.3)	47.7 (36.0)	219 (61.0)	39.2 (30.0)

^aExcludes one prescription for hydromorphone.

^bDoses in oral morphine equivalents.

^cRepresents the prescription claims that identified the resident as a LAO initiator.

monitoring is done to avoid the potential for adverse events.

There are important limitations to this study that need to be acknowledged. Chiefly, because this was a secondary data analysis of Medicaid claims data, it is impossible to ascertain how opioids were actually administered to patients following prescription. Furthermore, given limitations of this data source, it was impossible to evaluate clinical consequences of initiating LAOs in NH residents. Of note, some studies have suggested that transdermal fentanyl initiation in lower risk, younger patients is potentially safe.²¹

In conclusion, this study suggests that opioid-naïve initiation of LAOs in NH populations is common. Further research is required to determine if this practice is common in other regions and to quantify the risks of adverse events related to this practice. Given the significance of the U.S. FDA warning, including a “black box” warning with transdermal fentanyl, this rate of LAO initiation in opioid-naïve persons warrants efforts to improve the prescribing of opioids in NH residents, including quality improvement efforts, education of providers and NH staff, and greater monitoring of this potentially high-risk population.

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