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Longitudinal dose patterns among patients newly initiated on long-term opioid therapy in the United States, 2018 to 2019: an observational cohort study and time-series cluster analysis

S. Michaela Rikard[*],

Nisha Nataraj,

Kun Zhang,

Andrea E. Strahan,

Christina A. Mikosz,

Gery P. Guy Jr

Division of Overdose Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA, United States

Abstract

Opioid prescribing varies widely, and prescribed opioid dosages for an individual can fluctuate over time. Patterns in daily opioid dosage among patients prescribed long-term opioid therapy have not been previously examined. This study uses a novel application of time-series cluster analysis to characterize and visualize daily opioid dosage trajectories and associated demographic characteristics of patients newly initiated on long-term opioid therapy. We used 2018 to 2019 data from the IQVIA Longitudinal Prescription (LRx) all-payer pharmacy database, which covers 92% of retail pharmacy prescriptions dispensed in the United States. We identified a cohort of 277,967 patients newly initiated on long-term opioid therapy during 2018. Patients were stratified into 4 categories based on their mean daily dosage during a 90-day baseline period (<50, 50–89, 90–149, and ≥150 morphine milligram equivalent [MME]) and followed for a 270-day follow-up period. Time-series cluster analysis identified 2 clusters for each of the 3 baseline dosage categories

[*]Corresponding author. Address: Division of Overdose Prevention, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341, United States. Tel.: 770-488-0098. ruv4@cdc.gov (S. M. Rikard).

Author contributions: M.R., N.N., and K.Z. co-led the study conceptualization and design; M.R. and N.N. coled the development of methodology, data curation and analysis, and interpretation of results. M.R. led the formal analysis, visualization, and initial manuscript drafting and editing. A.S. and G.G. supported conceptualization and design. K.Z., A.S., and G.G. supported data curation and interpretation of results. G.G. supervised the study. N.N., K.Z., A.S., C.M., and G.G. assisted with manuscript drafting and editing. All authors approved the final manuscript as submitted.

Conflict of interest statement

The authors have no conflict of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B882.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

<150 MME and 3 clusters for the baseline dosage category ≥150 MME. One cluster in each baseline dosage category comprised opioid dosage trajectories with decreases in dosage at the end of the follow-up period (80.7%, 98.7%, 98.7%, and 99.0%, respectively), discontinuation (58.5%, 80.0%, 79.3%, and 81.7%, respectively), and rapid tapering (50.8%, 85.8%, 87.5%, and 92.9%, respectively). These findings indicate multiple clusters of patients newly initiated on long-term opioid therapy who experience discontinuation and rapid tapering and highlight potential areas for clinician training to advance evidence-based guideline-concordant opioid prescribing, including strategies to minimize sudden dosage changes, discontinuation, or rapid tapering, and the importance of shared decision-making.

Keywords

Long-term opioid therapy; Opioid prescribing; Cluster analysis

1. Introduction

In 2020, 91,799 drug overdose deaths occurred in the United States, reflecting a 31% increase from 2019.[13] Although synthetic opioids are increasingly involved in overdose deaths,[18] nearly 18% of the 68,630 opioid-involved overdose deaths in 2020 involved a prescription opioid, with over a 16% increase in prescription opioid-involved death rates from 2019 to 2020.[27,39] Although opioid prescribing rates have been declining since 2012, the duration of opioid prescriptions has increased.[10,11,24] Long-term opioid use is associated with increased risks of morbidity and mortality, including overdose. Even when taken as directed, prescription opioids have many physiologic effects including tolerance and physical dependence (ie, having symptoms of withdrawal with abrupt discontinuation or rapid dose reduction).[26,38] Although reducing exposure to opioids can reduce the risks of overdose and opioid use disorder, abrupt discontinuation and rapid tapering of opioid dosage among patients prescribed long-term opioid therapy have been linked with increased risk for fatal and nonfatal overdose, overdose involving heroin, mental health crisis events such as suicide attempts, and opioid-related emergency department visits or hospitalizations.[2,5,12,17]

Opioid prescribing varies widely by county,[10] which suggests a lack of consistency among clinicians when prescribing opioids. Prior research shows that there is a considerable amount of variation in opioids prescribed in clinical settings—by procedures,[14,36] by clinician specialty,[9] between medical centers,[34] and even across identical patient scenarios with the same clinical information.[33] Daily prescribed opioid dosages, measured by oral morphine milligram equivalents (MMEs), can vary substantially over time for a given individual. High-dose variability (measured as the standard deviation of MMEs over a period of time) has been found to be associated with increased risk of overdose compared with low-dose variability among patients prescribed long-term opioid therapy.[8]

Few studies have characterized and visualized trends in opioid dosage among patients prescribed long-term opioid therapy. The objective of this study is to identify and characterize patterns and variation in daily opioid dosage among patients newly initiated on long-term opioid therapy. To do so, we used a novel application of time-series cluster

analysis to study patients' daily opioid dosages over 12 months using a national retail pharmacy all-payer prescription dispensing database.

2. Methods

2.1. Data

This study used 2018 to 2019 data from the all-payer IQVIA Longitudinal Prescription (LRx) database. The database covers 92% of all retail pharmacy prescriptions in the United States, allowing us to capture patients' prescriptions longitudinally regardless of how prescriptions were paid. Opioids obtained through mail order or dispensed directly by clinicians, including methadone dispensed by opioid treatment programs, were not included in this database. We excluded buprenorphine formulations commonly used for treating opioid use disorder. We calculated oral MME using opioid conversion factors compiled by the Centers for Disease Control and Prevention (CDC) (National Center for Injury Prevention and Control, 2019 version).[23] We determined patients' total daily dosage of opioids for all prescriptions in the LRx database with corresponding MME conversion factors using data available on days' supply, prescription strength, dispensing date, and dispensed quantity.

2.2. Study population

The population of interest in this retrospective cohort study included patients who were newly initiated on long-term opioid therapy in 2018. Long-term opioid therapy was identified as those with ≥90% of days with a nonzero opioid dosage during a 90-day baseline period in 2018. To identify patients who were newly initiated on long-term therapy, we excluded patients who had an opioid prescription within a 365-day lookback period from their baseline period, based on the previous work.[31] By limiting our study population to newly initiated patients, we aimed to identify clear baseline dosages for long-term therapy and the potential impacts of baseline opioid dosage on dosage patterns throughout long-term opioid therapy. We followed each patient in the study cohort for an additional 270 days after their baseline period. Patients who received no opioid prescriptions during the follow-up period were retained in the study to allow us to identify potential opioid tapering and discontinuation. We excluded (1) patients aged <18 years; (2) patients with any prescriptions from oncology, palliative care, or hematology specialties during the 2018 to 2019 study period or within a 365-day lookback period before their first prescription to limit our population to patients with noncancer chronic pain; (3) patients with prescriptions of possibly erroneous daily quantities in solution (<1 unit per day) or 72-hour patch form (>1 unit every 3 days); and (4) patients with very low (<5 MME) or very high (>1000 MME) mean daily dosages during the baseline period to reduce the impact of outliers.

To improve cluster interpretability, patients were stratified into 4 categories based on their mean daily dosage during the baseline period (<50, 50–89, 90–149, and ≥150 MME), consistent with dosage categories defined in previous literature.[2,7,22] Next, a random sample of 10,000 patients was obtained from each of these baseline dosage categories to ensure computational feasibility of clustering algorithms. Construction of the study population and random sampling of each of the baseline dosage categories was performed using SAS

software (Version 9.4, SAS Institute Inc, Cary, NC). CDC determined institutional review board review and approval were not applicable because this research used deidentified secondary data.

2.3. Cluster analysis and validation

We conducted time-series cluster analysis of patients' opioid dosage trajectories using the partitioning around medoids (PAM) algorithm to identify patterns in opioid dosage among patients newly initiated on long-term opioid therapy across each of the 4 stratified baseline dosage categories. Time-series clustering is an unsupervised machine learning technique that is useful for identifying patterns and classifying individual time-series into distinct groups, or clusters, that are most similar.[1] Time-series data are inherently high dimensional, large data sets which can be difficult for clustering algorithms and require extensive computational times. We represented individual time series as 12 data points describing the monthly mean daily opioid dosage in MMEs to improve computational efficiency of the cluster analysis and smooth any inconsistencies in calculated daily MMEs within a month.

We chose the PAM algorithm for clustering because it is more robust to noise and selects a representative object or individual time series (ie, medoid) for each cluster identified.[16] In our application, the medoid represents the dosage trajectory of an actual patient in our analytic sample. Time-series clustering relies on a distance metric to determine the similarity of each time-series object in a cluster. We chose dynamic time warping (DTW) as the distance measure for clustering, which is a shape-based method for similarity measures.[1] Using this technique, individual time series are grouped based on patterns in their overall shape but may not be exactly aligned on the time axis.[4] Window size is a parameter of the DTW measure and refers to length of a sliding window on the time axis used to calculate the distance between individual time series.[29] We iteratively ran the PAM clustering algorithm with the number of clusters ranging from 2 to 6 and window size ranging from 1 to 3. The final parameters for number of clusters and window size were selected based on the highest average silhouette width, which is a combined validation measure that evaluates the similarity of time-series objects in a cluster as well as how distinct clusters are from one another.[16] Silhouette width values range from 0 to 1, with values around 0.7 or higher generally considered a strong clustering solution.[16,21] Analysis was performed on each analytic sample (n = 10,000) across the 4 baseline dosage categories in R version 4.1.1 (R Core Team, 2021)[28] using the package *dtwclust*[29] to perform the PAM clustering (function *tsclust*) and calculate cluster validity indices (function *cvi*). Sensitivity analysis on the number of clusters was conducted by performing PAM clustering on 10 random samples from each of the 4 baseline dosage categories and comparing the average silhouette width across all samples and number of clusters identified for each sample (determined by the highest average silhouette width).

2.4. Cluster summaries

2.4.1. Outcome measures—For each cluster that was identified by the PAM clustering algorithm, the average silhouette width for the cluster and the mean daily dosage in MMEs during the baseline period and follow-up period for patients in each cluster were reported. Two-tailed *t* tests were used to determine whether the difference in mean daily dosage

between 2 clusters was statistically significant and a 2-tailed 1-way analysis of variance was used for comparison of 3 or more clusters within a given baseline dosage category. In addition, the proportion of patients in each cluster who experienced the following outcomes during the follow-up period were reported: changes in daily opioid dosage (including increases, decreases, and stable dosages), discontinuation, and rapid tapering (defined below). Two-tailed Z tests were used to determine whether pairwise proportions were significantly different between clusters, and 2-tailed χ^2 tests were used for comparisons between 3 or more clusters within a given baseline dosage category.

Changes in daily opioid dosage were defined based on the percent change in the average daily dosage during the past 3 months of the follow-up period (months 10–12) compared with the average daily dosage during baseline (months 1–3). A percent change in dosage ≥ ±10% was classified as an increase or decrease in dosage, respectively, and < ±10% change was considered stable dosage. Discontinuation was defined as a 90-day window beginning at any point during the follow-up period with consecutive days of zero MME daily dosage. Rapid tapering was identified using an approach determined by Fenton et al.,[7] which calculates a rate of tapering based on the mean starting and ending dosages at 2 time points, and the corresponding duration of taper (see Appendix A, available as supplemental digital content at http://links.lww.com/PAIN/B882). According to the Department of Health & Human Services (HHS) Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics[37] and the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain,[6] a decrease of 10% of the original dose per week or slower (until approximately 30% of the original dose is reached, followed by a weekly decrease of approximately 10% of the remaining dose) is less likely to trigger withdrawal and can be successful for some patients, particularly when patients have taken opioids for weeks to months rather than years. Consistent with this guidance and previous studies,[7,22] rapid tapering was defined to be a dosage reduction of ≥40% overall monthly taper rate. This approach is less accurate as a measure of tapering rates when the initial opioid dosage is <50 MME. Therefore, rates of rapid tapering were not reported for patients with a baseline dosage <50 MME.

2.4.2. Demographics—Descriptive statistics were used to describe the demographics of patients (ie, sex, age, urban/rural classification, primary payer, and prescriber specialty) for each cluster identified by the PAM clustering algorithm. Urban/rural classification was determined using the prescriber's zip code, which is based on the prescriber's primary address, and classified using the 2013 National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme for Counties.[15] Primary payer and prescriber specialty were determined based on the most frequent payer type and prescriber specialty across all opioid prescriptions for an individual during the 12-month study period. Payment types captured in the LRx data were combined into 6 payer categories: private/commercial, self-pay, Medicaid, Medicare, assistance (eg, discount cards), and unknown (see Appendix B, available as supplemental digital content at http://links.lww.com/PAIN/B882). Demographics were summarized by the number and proportion of patients in each cluster.

3. Results

Among approximately 4.1 million patients who were prescribed long-term opioid therapy in 2018, we identified a study cohort of 277,967 patients who were newly initiated on long-term opioid therapy. Among patients newly initiated on long-term opioid therapy, 70.1% of patients were in the <50 MME baseline dosage category, 14.7% in the 50 to 89 MME category, 8.0% in the 90 to 149 MME category, and 7.2% in the ≥150 MME category (see Appendix C, available as supplemental digital content at http://links.lww.com/PAIN/B882). There were no significant differences noted in the demographics (ie, sex and age) of patients in the analytic sample compared with the corresponding population for each of the 4 baseline dosage categories. Results of the sensitivity analysis showed that the number of clusters identified was robust for baseline dosage categories <150 MME (2 clusters were identified for 9 of 10 random samples), whereas the number of clusters identified varied more substantially for the baseline dosage category ≥150 MME (see Appendix D, available as supplemental digital content at http://links.lww.com/PAIN/B882). For the analytic sample, cluster analysis identified 2 clusters for each of the baseline dosage categories <150 MME and 3 clusters for the baseline dosage category ≥150 MME (Table 1), and a window size of 2 months was selected based on the highest average silhouette width across all analyses.

As noted in Table 1, for the baseline dosage category (A) <50 MME, patients in cluster A1 had a lower mean daily dosage during the baseline period (18.5 MME) compared with patients in cluster A2 (32.0 MME) and were more likely to experience decreases in daily dosage (80.7%) and discontinuation (58.5%) during the follow-up period compared with patients in cluster A2 (32.6% and 11.3%, respectively). More patients in cluster A2 had a stable dosage (42.2%) or increase in daily dosage (25.2%) during the follow-up period compared with patients in cluster A1 (12.3% and 7.0%, respectively). The average silhouette width was higher for cluster A1 (0.65) compared with A2 (0.33), indicating more heterogeneity of the individual dosage trajectories in cluster A2.

For baseline dosage categories (B) 50 to 89 MME and (C) 90 to 149 MME, patients in both sets of clusters identified (B1 and B2; C1 and C2) had similar mean daily dosages during the baseline period. Nearly all patients in clusters B1 and C1 experienced a decrease in daily dosage during the follow-up period (98.7% and 98.7%, respectively), whereas nearly half of the patients in clusters B2 and C2 retained stable dosages (44.7% and 44.6%, respectively). Some patients in clusters B2 and C2 also experienced increases in daily dosage (18.8% and 16.3%, respectively) or decreases in daily dosage (36.5% and 39.1%, respectively) during the follow-up period. Approximately 4 in 5 patients in clusters B1 and C1 experienced discontinuation (80.0% and 79.3%, respectively) or rapid tapering (85.8% and 87.5%, respectively). The average silhouette widths for clusters B1 and C1 (0.62 and 0.59, respectively) were higher than clusters B2 and C2 (0.47 and 0.48 respectively), indicating more heterogeneity in the dosage trajectories of patients in clusters B2 and C2.

Three distinct clusters of patients were identified for the baseline dosage category (D) ≥150 MME, where patients in Cluster D3 had a notably higher mean daily dosage during the baseline period (382.0 MME) compared with patients in clusters D1 and D2 (231.2 and

202.1, respectively). Similar trends were observed in cluster D1 as seen in the 50 to 89 and 90 to 149MME dosage categories, where 99.0% of patients in this cluster experienced decreases in daily dosage during the follow-up period, 81.7% experienced discontinuation, and 92.9% experienced rapid tapering. Approximately 2 in 5 patients in clusters D2 and D3 had stable daily dosages during the follow-up period (38.7% and 44.5%, respectively) and slightly more patients in cluster D3 experienced an increase in dosage (17.4%) compared with cluster D2 (10.2%). Discontinuation and rapid tapering were not common among patients in these 2 clusters. The average silhouette width for cluster D3 was particularly low (0.15), indicating a high degree of heterogeneity in individual trajectories at these highest daily dosages.

The dosage trajectories for all individual time series along with the representative medoid (representing the mean monthly dosages of an actual patient) of each cluster for all baseline dosage categories are displayed in Figures 1A–D. Although individual trajectories demonstrated a high degree of heterogeneity, the representative medoids for clusters A-D1 exhibit consistent tapering and discontinuation around month 6. The medoids for clusters A-D2 exhibit some fluctuations in dosage, but overall remain stable during the follow-up period. Overall, some patients across these clusters experience increases in dosage and others experience tapering and discontinuation. The dosage trajectories in cluster D3 for the baseline dosage category ≥150 MME exhibit a high degree of heterogeneity and high mean daily dosages.

The percentage of cluster members experiencing discontinuation during the follow-up period for each baseline dosage category is presented in Figures 2A–D, where the first month of a 90-day discontinuation is reported. Across all baseline dosage categories, more patients in clusters A-D1 experienced discontinuation, which was more likely to occur early during the follow-up period. Conversely, fewer patients in clusters A-D2 (and cluster D3 for baseline dosage category ≥150 MME) experienced discontinuation, more frequently occurring later in the follow-up period.

The characteristics of patients (sex, age, urban/rural classification, primary payer, and prescriber specialty) who were newly initiated on long-term opioid therapy in 2018, stratified by mean baseline daily dosage and cluster are described in Table 2. For the baseline dosage category <50 MME, there were more females in cluster A1 (58.5%) compared with cluster A2 (55.8%). For the baseline dosage categories 50 to 89 and ≥150 MME, there were more females in cluster B2 (55.6%) compared with cluster B1 (52.9%) and in cluster D2 (50.8%) compared with clusters D1 (48.1%) and D3 (47.2%). There were no significant differences in sex between clusters for the baseline dosage category 90 to 149 MME. There were more patients in the 36 to 65 age group in clusters A-D2 and cluster D3 (69.7%, 70.1%, 73.0%, 74.6%, and 79.1%, respectively) compared with clusters A-D1 (56.7%, 67.4%, 70.9%, and 71.6%, respectively). For the baseline dosage category <50 MME, there were more patients in the ≥66 age group in Cluster A1 (35.1%) compared with cluster A2 (23.3%). The only significant difference in urban/rural classification between clusters was noted for the baseline dosage category 50 to 89 MME, where there were more patients in the micropolitan classification in cluster B2 (9.9%) compared with cluster B1 (8.6%). Medicare was the most common primary payer across all baseline dosage

categories, followed by private insurance and Medicaid. There were no differences noted in Medicare for the baseline dosage category <50 MME, but for all other dosage categories, Medicare was more common in clusters B-D2 and cluster D3 (42.7%, 43.8%, 42.8%, and 45.1%, respectively) compared with clusters B-D1 (36.0%, 37.1%, and 34.5%, respectively). Medicaid was more prevalent in clusters B1 and C1 (15.1% and 13.5%) compared with clusters B2 and C2 (13.5% and 11.5%). There were no significant differences noted in the prevalence of private insurance between clusters for all baseline dosage categories. Self-pay and assistance were more prevalent in clusters B-D1 (self-pay: 6.0%, 8.3%, and 13.0%; assistance: 8.0%, 7.1%, and 7.3%) compared with clusters B-D2 (self-pay: 4.0%, 5.6%, and 8.3%; assistance: 5.6%, 5.7%, and 5.3%), and self-pay was more prevalent in cluster A1 (5.4%) compared with cluster A2 (4.1%). Notable differences in prescriber specialty included that across all baseline dosage categories, primary care was more prevalent in clusters A-D1 and D3 (47.2%, 33.7%, 33.7%, 37.7%, and 39.5%, respectively) compared with clusters A-D2 (39.0%, 31.2%, 30.6%, and 34.8%, respectively). The advanced practitioner specialty, which includes nurse practitioners and physician assistants, was more prevalent in clusters A-D2 (24.4%, 28.5%, 27.6%, and 22.1%, respectively) compared with clusters A-D1 and D3 (21.0%, 25.2%, 24.1%, 17.2%, and 15.5%, respectively). Pain medicine was more prevalent in cluster A2 (20.9%) compared with cluster A1 (13.4%), but no significant differences were noted for baseline dosage categories >50 MME.

4. Discussion

The objective of this study was to identify and characterize variations in daily opioid dosage among adults newly initiated on long-term opioid therapy. Time-series cluster analysis identified 9 clusters of dosage trajectories across 4 baseline dosage categories. Decreases in daily opioid dosage, discontinuation, and rapid tapering occurred frequently for one cluster of patients among each baseline dosage category (clusters A-D1). For baseline categories >50 MME, nearly all patients (>98%) in clusters B-D1 experienced decreases in dosage at the end of the follow-up period, approximately 4 in 5 patients (79%−82%) experienced discontinuation, and approximately 9 in 10 patients (86%−93%) experienced rapid tapering among these clusters. Furthermore, the size of these clusters (clusters B-D1) was consistent across baseline dosage categories, representing 35% to 38% of the analytic sample in these categories. Other studies have reported increasing rates of discontinuation[20] and tapering[7] in recent years among patients receiving high-dose long-term opioid therapy. Our findings are consistent with those of Stein et al.[30] which reported a high rate of rapid tapering and discontinuation among patients newly initiated on high-dose opioid therapy. Although patients who are newly initiated on long-term opioid therapy are a relatively small proportion (1%) of all patients newly prescribed opioids,[30,40] our findings indicate high rates of discontinuation and rapid tapering in this population, particularly among those prescribed daily dosages >50 MME.

Among the remaining clusters (clusters A-D2, and D3), 39% to 45% of patients in these clusters experienced stable dosage, whereas 10% to 25% of patients experienced increases in dosage and 33% to 51% experienced decreases in dosage at the end of the follow-up period. This was also indicated by the lower average silhouette widths for these clusters, which signals more heterogeneity in the dosage trajectories than can be explained within a

single cluster. Heterogeneity in dosage trajectories was most notable among patients with the highest mean daily dosages (cluster D3), where the average silhouette coefficient was the lowest among all clusters identified. In addition, sensitivity analysis demonstrated that the number of clusters was not robust in the ≥150 MME baseline dosage category because of a high degree of heterogeneity in individual dosage trajectories. Among patients in cluster D3 who experienced the highest mean daily dosages (average daily dosage during baseline of 382.0 MME), 17.4% experienced increases in dosage at the end of the follow-up period. This finding highlights a specific area of high-risk prescribing that could inform targeted education and training for clinicians related to guideline concordant prescribing. There is considerable heterogeneity in the dosage trajectories of patients with very high daily opioid dosages. For certain patients or clinical scenarios, periods of long-term opioid use followed by taper or discontinuation in dosage may be clinically appropriate; however, these data do not provide these clinical characteristics. Further research that includes more clinical information about patients (eg, diagnoses, patient history, and outcomes) could help understand prescribing patterns in this population.

When comparing the demographic characteristics of patients in each cluster, a noteworthy finding was that Medicare was more prevalent in clusters likely to experience stable dosages and less frequent discontinuation or tapering for baseline dosage categories >50 MME (clusters B2-D2 and D3), despite similar proportions of patients aged ≥66 years in these clusters. Conversely, Medicaid, assistance programs, and self-pay were more prevalent among clusters likely to experience dosage decreases, discontinuation, and tapering. There were no differences noted in the prevalence of private insurance between clusters. One possible hypothesis for these findings is that patients paying out-of-pocket or through assistance programs may experience cost barriers that prevent them from accessing the prescriptions needed to manage their pain, or scrutiny from clinicians who may be concerned about the increased likelihood of multiple prescriber episodes and opioid misuse.[3,19] Another possible hypothesis, specifically for patients with Medicaid coverage, is that these patients experience frequent disruptions, or move in and out of Medicaid coverage, which may contribute to discontinuation of prescriptions.[32]

An additional finding of interest was that for baseline dosage categories <150 MME, primary care prescriber specialty was more prevalent in clusters likely to experience dosage decreases, discontinuation, and tapering, whereas the advanced practitioner specialty (nurse practitioners and physician assistants) was more prevalent among clusters likely to experience stable dosages and less frequent discontinuation or tapering. This finding is consistent with that of Stein et al.[30] who reported that rapid discontinuation was less likely for new, long-term, high-dosage opioid treatment episodes with advanced practitioners compared with primary care clinicians.

This study is subject to several limitations. First, these data do not include clinical information about patients such as diagnosis, patient history, or adverse outcomes including emergency department visits or hospitalizations related to substance use disorder or overdose or loss to follow-up due to fatal overdose or death from other causes. Therefore, we cannot draw conclusions about why long-term opioid therapy has been prescribed or comment on the individual risk-benefit considerations related to dosage increases, decreases,

tapering, or discontinuation potentially initiated in response to adverse events. Second, consistent with other clustering analyses, the results are dependent on the clustering algorithm and parameters chosen such as distance metric, window size, and cluster validation indices, although these parameters were varied and chosen based on clustering results with the highest validation indices. Third, we were limited to a representative sample of patients among each baseline dosage category to maintain computational feasibility for the cluster analysis. Sensitivity analyses of additional samples showed that the number of clusters identified was robust for baseline dosage categories <150 MME but was not robust for baseline dosages ≥150 MME due to a high degree of heterogeneity in dosage trajectories among these patients. Finally, we cannot differentiate patients who were potentially lost to follow-up due to adverse events, such as fatal overdose or death from other causes, or received opioids from pharmacies not included in the IQVIA LRx database, such as mail order prescription services or pharmacies operated by health maintenance organizations, hospitals, or long-term inpatient care facilities.[35]

Despite these limitations in the data, the IQVIA LRx database is an all-payer pharmaceutical claims database covering over 92% of all retail prescriptions in the United States and allows us to track patients regardless of payer, including cash payments. This study makes important contributions to our understanding of prescribing patterns for patients newly initiated on long-term opioid therapy and is the first, to the best of our knowledge, to conduct cluster analysis of opioid dosage for patients on long-term opioid therapy, thereby helping to visualize and characterize recent patterns in opioid prescribing. While opioid prescribing has declined in recent years, it varies widely by demographic, geographic, and clinical factors.[9–11,14,24,33,34,36] This cluster analysis characterizes unique patterns that exist in dosage trajectories and associated demographic characteristics among patients newly initiated on long-term opioid therapy. These results can help inform future studies of opioid prescribing patterns by providing increased understanding of the heterogeneity that exists in prescribed opioid dosage at the individual level and highlights the need for additional research to describe heterogeneity that exists in dosage trajectories of individuals newly initiated on long-term opioid therapy with high daily dosages (≥150 MME).

Results of this cluster analysis identified clusters of patients who were newly initiated on long-term opioid therapy with dosage trajectories characterized by frequent discontinuation and rapid tapering across all baseline dosage categories but which occurred more frequently for patients with daily dosages >50 MME. These findings provide insight about patterns in prescribed opioid dosage among individuals newly initiated on long-term opioid therapy and highlight opportunities for clinician training pertaining to guideline-concordant opioid prescribing, including the risks of high-dose opioid prescribing and the importance of patient-centric care when initiating dosage changes for patients receiving long-term opioid therapy.[6,37] According to the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain, unless there is a life-threatening issue such as warning signs of an imminent overdose, the benefits of rapidly tapering or abruptly discontinuing opioids are unlikely to outweigh the substantial risks of these practices to patients.[6] Clinicians should carefully weigh both the benefits and risks of continuing opioid medications and the benefits and risks of tapering opioids.[6] In situations where benefits and risks of continuing opioids are considered to be close or unclear, shared decision-making with patients is particularly

important.[6] Clinical tools and training exist to aid clinicians in weighing the risks and benefits when prescribing opioids for chronic pain, and recommendations regarding nonopioid and nonpharmacologic pain management therapies.[25] Opportunities remain to improve guideline-concordant opioid prescribing, tapering, and discontinuation to ensure safer, evidence-based treatment of pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability:

The original data used in this analysis were obtained from IQVIA. IQVIA has restrictions prohibiting the authors from making the data publicly available. Interested researchers may contact IQVIA to gain access to the data.

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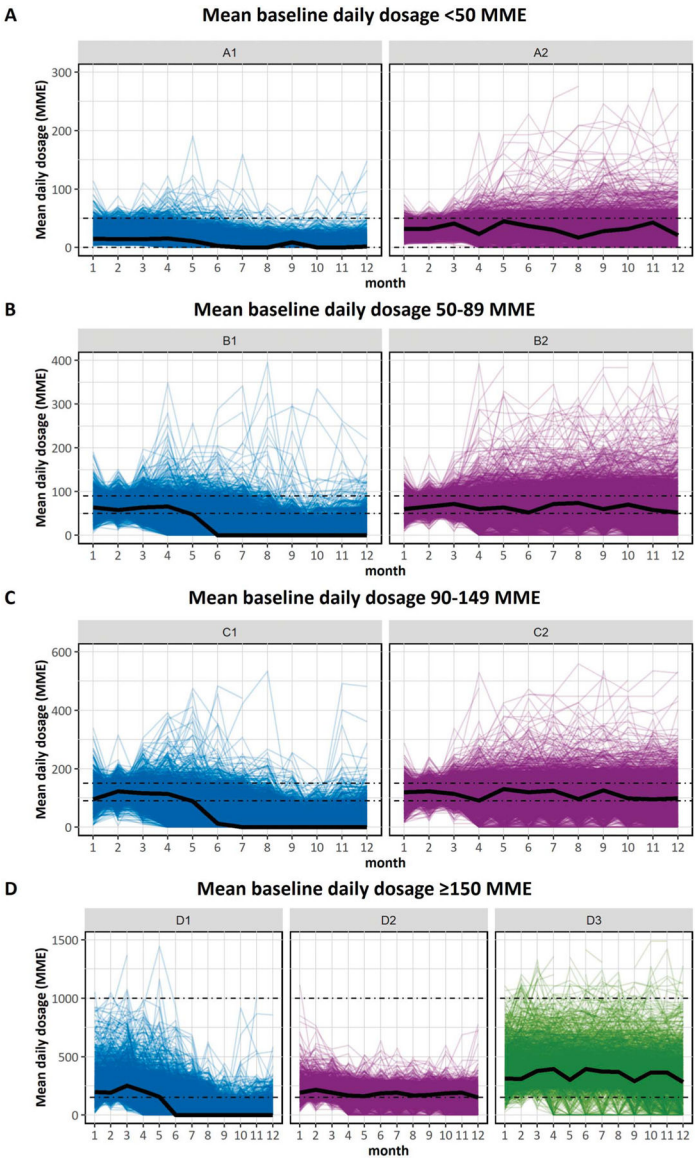

Figure 1.

Monthly mean daily dosages during a 90-day baseline period (months 1–3) and 270-day follow-up period (months 4–12) for all individual time-series trajectories contained within each cluster resulting from the PAM clustering algorithm for baseline dosage categories (A) <50 MME, (B) 50–89 MME, (C) 90–149 MME, and (D) ≥150 MME. Solid black line = cluster medoid. Dashed black lines = upper and lower bounds of mean daily baseline dosage used for stratification. Note: y-axes upper limits vary due to wide range in daily dosages across baseline dosage categories. Data source: IQVIA Longitudinal Prescription (LRx) retail pharmacy database, 2018–2019.

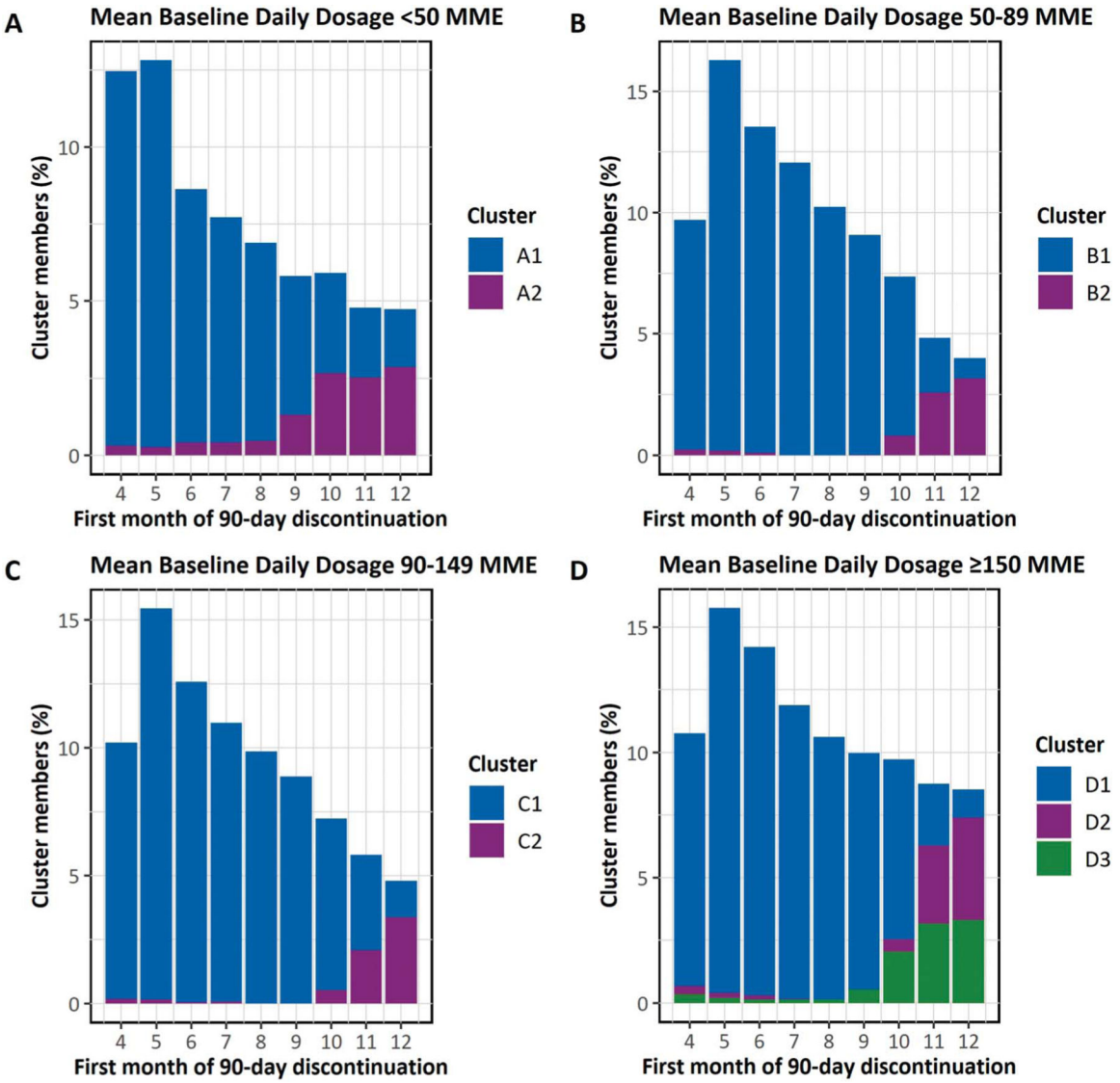

Figure 2.

Percentage of cluster members experiencing a period of 90-day discontinuation of opioid dosage during the follow-up period (months 4–12) for baseline dosage categories (A) <50 MME, (B) 50–89 MME, (C) 90–149 MME, and (D) ≥150 MME. If patients experience more than 90 days of discontinuation or multiple periods of 90-day discontinuation, only the first occurrence of this event was captured. Data source: IQVIA Longitudinal Prescription (LRx) retail pharmacy database, 2018–2019.

Table 1

Characteristics of clusters identified by partitioning around medoids clustering algorithm, by mean baseline daily dosage, 2018 to 2019.

	Mean baseline daily dosage								
	<50 MME		**50–89 MME**		**90–149 MME**		**≥150 MME**		
	Cluster A1	**Cluster A2**	**Cluster B1**	**Cluster B2**	**Cluster C1**	**Cluster C2**	**Cluster D1**	**Cluster D2**	**Cluster D3**
	n = 5949	**n = 4051**	**n = 3793**	**n = 6207**	**n = 3809**	**n = 6191**	**n = 3467**	**n = 4486**	**n = 2047**
	59.5%	**40.5%**	**37.9%**	**62.1%**	**38.1%**	**61.9%**	**34.7%**	**44.9%**	**20.5%**
Clustering indices									
Avg. silhouette width	0.65	0.33	0.62	0.47	0.59	0.48	0.47	0.53	0.15
Daily dosage MME, mean (95% CI)									
Baseline period	**18.5 (18.3–18.8)**	**32.0 (31.7–32.3)**	**65.1 (64.8–65.5)**	**66.1 (65.9–66.4)**	**111.7 (111.2–112.3)**	**114.0 (113.5–114.4)**	**231.2 (228.1–234.3)**	**202.1 (200.8–203.4)**	**382.0 (376.0–388.1)**
Follow-up period	**7.3 (7.2–7.5)**	**31.7 (31.3–32.1)**	**19.1 (18.6–19.6)**	**64.9 (64.3–65.5)**	**33.8 (33.0–34.6)**	**108.9 (108.1–109.7)**	**64.4 (62.6–66.1)**	**175.7 (174.5–176.8)**	**358.0 (352.5–363.6)**
Outcome measures, N (%)									
Dosage changes									
Decrease [*]	**4801 (80.7%)**	**1322 (32.6%)**	**3742 (98.7%)**	**2266 (36.5%)**	**3760 (98.7%)**	**2421 (39.1%)**	**3433 (99.0%)**	**2295 (51.2%)**	**781 (38.2%)**
Stable [†]	**729 (12.3%)**	**1708 (42.2%)**	**29 (0.8%)**	**2773 (44.7%)**	**36 (0.9%)**	**2763 (44.6%)**	**29 (0.8%)**	**1735 (38.7%)**	**910 (44.5%)**
Increase [‡]	**419 (7.0%)**	**1021 (25.2%)**	**22 (0.6%)**	**1168 (18.8%)**	**13 (0.3%)**	**1007 (16.3%)**	**5 (0.1%)**	**456 (10.2%)**	**356 (17.4%)**
Discontinuation [§]	**3479 (58.5%)**	**456 (11.3%)**	**3035 (80.0%)**	**439 (7.1%)**	**3021 (79.3%)**	**400 (6.5%)**	**2834 (81.7%)**	**377 (8.4%)**	**206 (10.1%)**
Rapid tapering [‖]	—[¶]	—[¶]	**3255 (85.8%)**	**373 (6.0%)**	**3333 (87.5%)**	**455 (7.3%)**	**3221 (92.9%)**	**536 (11.9%)**	**307 (15.0%)**

Boldface text indicates statistical significance ($P < 0.05$) between clusters for each baseline dosage category.

Data source: IQVIA Longitudinal Prescription (LRx) retail pharmacy database, 2018 to 2019.

[*] Defined as ≥10% decrease in mean daily dosage during the past 3 months of the follow-up period compared with baseline.

[†] Defined as < ±10% change in mean daily dosage during the past 3 months of the follow-up period compared with baseline.

[‡] Defined as ≥10% increase in mean daily dosage during the past 3 months of the follow-up period compared with baseline.

[§] Defined as a 90-day window with consecutive days of zero MME daily dosage.

[‖] Defined as a dosage reduction of ≥40% overall monthly taper rate.

[¶] Rapid tapering is not reported for patients with a baseline dosage <50 MME due to concerns about the accuracy of calculating tapering rates at low dosages.

CI, confidence interval; MME, oral morphine milligram equivalent; PAM, partitioning around medoids.

Table 2

Characteristics of adults newly initiated on long-term opioid therapy, by mean baseline daily dosage and cluster, 2018 to 2019.

Individual characteristic	Mean baseline daily dosage, N (%)								
	<50 MME		50–89 MME		90–149 MME		≥150 MME		
	Cluster A1 n = 5949 59.5%	Cluster A2 n = 4051 40.5%	Cluster B1 n = 3793 37.9%	Cluster B2 n = 6207 62.1%	Cluster C1 n = 3809 38.1%	Cluster C2 n = 6191 61.9%	Cluster D1 n = 3467 34.7%	Cluster D2 n = 4486 44.9%	Cluster D3 n = 2047 20.5%
Sex									
Male	**2444 (41.1%)**	**1782 (44.0%)**	**1770 (46.7%)**	**2740 (44.1%)**	1796 (47.2%)	2932 (47.4%)	**1777 (51.3%)**	**2190 (48.8%)**	**1074 (52.5%)**
Female	**3482 (58.5%)**	**2261 (55.8%)**	**2008 (52.9%)**	**3453 (55.6%)**	1996 (52.4%)	3234 (52.2%)	**1666 (48.1%)**	**2277 (50.8%)**	**967 (47.2%)**
Age group (y)									
18–35	**484 (8.1%)**	**281 (6.9%)**	**378 (10.0%)**	**384 (6.2%)**	**382 (10.0%)**	**388 (6.3%)**	**324 (9.3%)**	**286 (6.4%)**	**99 (4.8%)**
36–65	**3374 (56.7%)**	**2825 (69.7%)**	**2556 (67.4%)**	**4354 (70.1%)**	**2699 (70.9%)**	**4519 (73.0%)**	**2481 (71.6%)**	**3345 (74.6%)**	**1620 (79.1%)**
≥66	**2091 (35.1%)**	**945 (23.3%)**	859 (22.6%)	1469 (23.7%)	728 (19.1%)	1284 (20.7%)	**662 (19.1%)**	**855 (19.1%)**	**328 (16.0%)**
Urban/rural classification									
Metropolitan	4999 (84.0%)	3375 (83.3%)	3293 (86.8%)	5334 (85.9%)	3381 (88.8%)	5463 (88.2%)	3122 (90.0%)	4043 (90.1%)	1865 (91.1%)
Micropolitan	558 (9.4%)	428 (10.6%)	**325 (8.6%)**	**613 (9.9%)**	288 (7.6%)	497 (8.0%)	229 (6.6%)	298 (6.6%)	116 (5.7%)
Noncore	392 (6.6%)	248 (6.1%)	175 (4.6%)	260 (4.2%)	140 (3.7%)	231 (3.7%)	116 (3.3%)	145 (3.2%)	66 (3.2%)
Payer *									
Medicare	2295 (38.6%)	1606 (39.6%)	**1364 (36.0%)**	**2651 (42.7%)**	**1412 (37.1%)**	**2709 (43.8%)**	**1195 (34.5%)**	**1920 (42.8%)**	**924 (45.1%)**
Medicaid	903 (15.2%)	661 (16.3%)	**572 (15.1%)**	**841 (13.5%)**	**514 (13.5%)**	**712 (11.5%)**	362 (10.4%)	463 (10.3%)	213 (10.4%)
Assistance	355 (6.0%)	242 (6.0%)	**302 (8.0%)**	**350 (5.6%)**	**271 (7.1%)**	**355 (5.7%)**	**252 (7.3%)**	**239 (5.3%)**	**96 (4.7%)**
Private	1515 (25.5%)	1003 (24.8%)	959 (25.3%)	1577 (25.4%)	932 (24.5%)	1535 (24.8%)	816 (23.5%)	1094 (24.4%)	476 (23.3%)
Self-pay	**319 (5.4%)**	**165 (4.1%)**	**228 (6.0%)**	**246 (4.0%)**	**316 (8.3%)**	**346 (5.6%)**	**451 (13.0%)**	**371 (8.3%)**	**152 (7.4%)**
Unknown	450 (7.6%)	339 (8.4%)	310 (8.2%)	493 (7.9%)	314 (8.2%)	493 (8.0%)	**343 (9.9%)**	**375 (8.4%)**	**173 (8.5%)**
Prescriber specialty †									
Primary care	**2810 (47.2%)**	**1581 (39.0%)**	**1280 (33.7%)**	**1935 (31.2%)**	**1283 (33.7%)**	**1892 (30.6%)**	**1308 (37.7%)**	**1561 (34.8%)**	**808 (39.5%)**
Advanced practitioner	**1247 (21.0%)**	**988 (24.4%)**	**954 (25.2%)**	**1772 (28.5%)**	**918 (24.1%)**	**1706 (27.6%)**	**598 (17.2%)**	**992 (22.1%)**	**317 (15.5%)**
Pain medicine	**799 (13.4%)**	**847 (20.9%)**	864 (22.8%)	1501 (24.2%)	947 (24.9%)	1553 (25.1%)	862 (24.9%)	1094 (24.4%)	537 (26.2%)

Boldface text indicates statistical significance ($P < 0.05$) between clusters for each baseline dosage category.

Data source: IQVIA Longitudinal Prescription (LRx) retail pharmacy database, 2018 to 2019.

[*] For detailed descriptions of payer categories, see Appendix B, available as supplemental digital content at http://links.lww.com/PAIN/B882.

[†] Only the top 3 most frequent prescriber specialties are reported. "Advanced practitioner" includes nurse practitioner and physician assistant. "Primary care" includes internal medicine, family medicine, and preventative medicine.

MME, oral morphine milligram equivalent.