ORIGINAL RESEARCH

Characterizing Opioid Response in Older Veterans in the Post-Acute Setting

Victoria D. Powell, MD[a,b]; Christine T. Cigolle, MD[a,b]; Neil B. Alexander, MD[a,b]; Robert V. Hogikyan, MD, MPH[a,b]; April D. Bigelow, PhD, AGPCNP-BC[c]; and Maria J. Silveira, MD, MA, MPH[a,b]

Background: Opioids often are used in post-acute care (PAC) settings, although there is a lack of evidence of sustained pain reduction and improved function. There are subgroups of individuals whose pain does not respond well to opioids yet report these agents as highly beneficial. We aimed to classify opioid responsiveness among veterans residing in a US Department of Veterans Affairs community living center PAC unit.

Methods: This observational, cross-sectional study used barcode medication administration data followed by retrospective chart review. We determined opioid responsiveness along a continuum during 4 nonconsecutive days in 2016 and 2017. We defined opioid responsiveness as the mean change in pre- and postopioid pain ratings using the 0 to 10 scale over the 24-hour observation period (ie, mean Δ score). The chart review identified correlates of opioid responsiveness adjusting for mean pre-opioid pain ratings.

Results: Among the 41 residents who received opioids for at least moderate pain (≥ 4 of 10), the average response was highly variable (range, 0.5 - 6.3). Response did not correlate with demographic variables, indication for admission, or medical comorbidities, including cancer diagnosis. The presence of any psychiatric diagnosis (P = .03), pain service consult (P = .03), and higher opioid dosage (P = .002) was significantly associated with poorer response.

Conclusions: This pilot study classified opioid response on a continuum using a scalable administrative data source. Despite receiving higher dosages and more specialist consultations, some veterans' pain responds poorly to opioids. Psychiatric comorbidity seems to increase this risk. Future studies in larger, more representative populations are necessary to confirm these findings to develop personalized pain management strategies that mitigate risks of opioids.

Author affiliations can be found at the end of the article.
Correspondence: Victoria D. Powell (powellvd@med.umich.edu)

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Older adults admitted to post-acute settings frequently have complex rehabilitation needs and multimorbidity, which predisposes them to pain management challenges.[1,2] The prevalence of pain in post-acute and long-term care is as high as 65%, and opioid use is common among this population with 1 in 7 residents receiving long-term opioids.[3,4]

Opioids that do not adequately control pain represent a missed opportunity for deprescribing. There is limited evidence regarding efficacy of long-term opioid use (> 90 days) for improving pain and physical functioning.[5] In addition, long-term opioid use carries significant risks, including overdose-related death, dependence, and increased emergency department visits.[5] These risks are likely to be pronounced among veterans receiving post-acute care (PAC) who are older, have comorbid psychiatric disorders, are prescribed several centrally acting medications, and experience substance use disorder (SUD).[6]

Older adults are at increased risk for opioid toxicity because of reduced drug clearance and smaller therapeutic window.[5] Centers for Disease Control and Prevention (CDC) guidelines recommend frequently assessing patients for benefit in terms of sustained improvement in pain as well as physical function.[5] If pain and functional improvements are minimal, opioid use and nonopioid pain management strategies should be considered. Some patients will struggle with this approach. Directly asking patients about the effectiveness of opioids is challenging. Opioid users with chronic pain frequently report problems with opioids even as they describe them as indispensable for pain management.[7,8]

Earlier studies have assessed patient perspectives regarding opioid difficulties as well as their helpfulness, which could introduce recall bias. Patient-level factors that contribute to a global sense of distress, in addition to the presence of painful physical conditions, also could contribute to patients requesting opioids without experiencing adequate pain relief. One study in veterans residing in PAC facilities found that individuals with depression, posttraumatic stress disorder (PTSD), and SUD were more likely to report pain and receive scheduled analgesics; this effect persisted in individuals with PTSD even after adjusting for demographic and functional status variables.[9] The study looked only at analgesics as a class and did not examine opioids specifically. It is possible that distressed individuals, such as those with uncontrolled

depression, PTSD, and SUD, might be more likely to report high pain levels and receive opioids with inadequate benefit and increased risk. Identifying the primary condition causing distress and targeting treatment to that condition (ie, depression) is preferable to escalating opioids in an attempt to treat pain in the context of nonresponse. Assessing an individual's aggregate response to opioids rather than relying on a single self-report is a useful addition to current pain management strategies.

The goal of this study was to pilot a method of identifying opioid-nonresponsive pain using administrative data, measure its prevalence in a PAC population of veterans, and explore clinical and demographic correlates with particular attention to variates that could indicate high levels of psychological and physical distress. Identifying pain that is poorly responsive to opioids would give clinicians the opportunity to avoid or minimize opioid use and prioritize treatments that are likely to improve the resident's pain, quality of life, and physical function while minimizing recall bias. We hypothesized that pain that responds poorly to opioids would be prevalent among veterans residing in a PAC unit. We considered that veterans with pain poorly responsive to opioids would be more likely to have factors that would place them at increased risk of adverse effects, such as comorbid psychiatric conditions, history of SUD, and multimorbidity, providing further rationale for clinical equipoise in that population.[6]

METHODS

This was a small, retrospective cross-sectional study using administrative data and chart review. The study included veterans who were administered opioids while residing in a single US Department of Veterans Affairs (VA) community living center PAC (CLC-PAC) unit during at least 1 of 4 nonconsecutive, random days in 2016 and 2017. The study was approved by the institutional review board of the Ann Arbor VA Health System (#2017-1034) as part of a larger project involving models of care in vulnerable older veterans.

Inclusion criteria were the presence of at least moderate pain (≥ 4 on a 0 to 10 scale); receiving ≥ 2 opioids ordered as needed over the prespecified 24-hour observation period; and having ≥ 2 pre-and postopioid administration pain scores during the observation period. Veterans who did not meet these criteria were excluded. At the time of initial sample selection, we did not capture information related to coprescribed analgesics, including a standing order of opioids. To obtain the sample, we initially characterized all veterans on the 4 days residing in the CLC-PAC unit as those reporting at least moderate pain (≥ 4) and those who reported no or mild pain (< 4). The cut point of 4 of 10 is consistent with moderate pain based on earlier work showing higher likelihood of pain that interferes with physical function.[10] We then restricted the sample to veterans who received ≥ 2 opioids ordered as needed for pain and had ≥ 2 pre- and postopioid administration numeric pain rating scores during the 24-hour observation period. This methodology was chosen to enrich our sample for those who received opioids regularly for ongoing pain. Opioids were defined as full μ-opioid receptor agonists and included hydrocodone, oxycodone, morphine, hydromorphone, fentanyl, tramadol, and methadone.

Medication administration data were obtained from the VA corporate data

FIGURE 1 Flow Diagram for Post-Acute Care Patients Receiving As-Needed Opioids

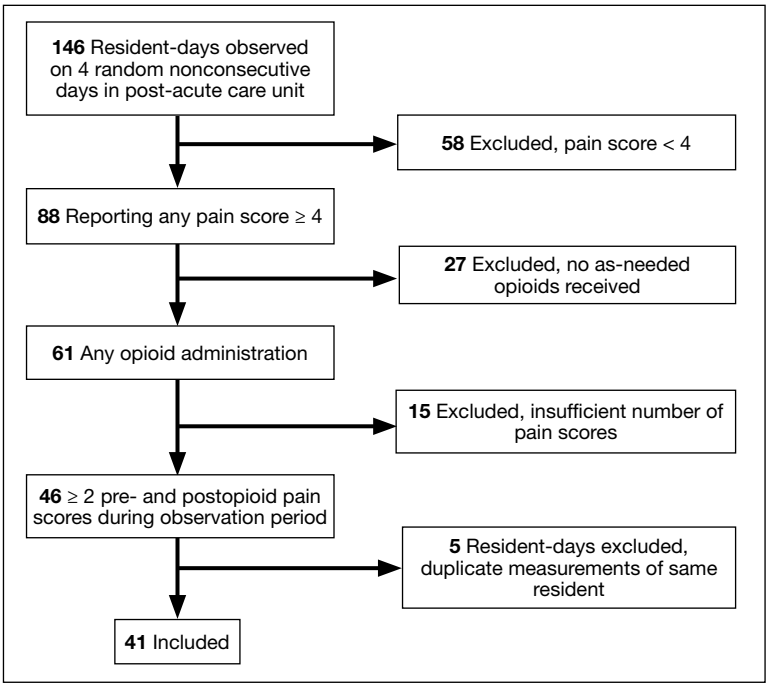


Table Participant Characteristics (N = 41)

Characteristics	Results
Age, mean (SD), y	63.8 (7.23)
Sex, No. (%)	
Male	38 (92.7)
Female	3 (7.3)
Race, No. (%)	
White	31 (75.6)
Black	4 (9.8)
Unknown or declined	6 (14.6)
Ethnicity, No. (%)	
Hispanic	1 (2.4)
Non-Hispanic	39 (95.1)
Unknown or declined	1 (2.4)
Marital status, No. (%)	
Married	13 (31.7)
Never married	5 (12.2)
Divorced	18 (43.9)
Widowed	5 (12.2)
Indication for postacute admission, No. (%)	
Wound care	17 (41.5)
Skilled rehabilitation	15 (36.6)
IV antibiotics	7 (17.1)
Radiation therapy	6 (14.6)
Other	2 (4.8)
Medical comorbidities, No. (%)[a]	
Congestive heart failure	8 (19.5)
Chronic obstructive pulmonary disease	13 (31.7)
Active cancer	10 (24.4)
Cancer, in remission	8 (19.5)
Other	2 (4.8)
Psychiatric disorder, any, No. (%)	25 (61.0)
Mood disorder	22 (53.7)
Anxiety disorder	5 (12.2)
Psychotic disorder	3 (7.3)
Posttraumatic stress disorder	4 (9.8)

Characteristics	Results
Substance use disorder, No. (%)	
Active	17 (41.5)
Excluding tobacco/nicotine	3 (7.3)
In remission	26 (63.4)
Excluding tobacco/nicotine	19 (46.3)
Consults suggesting distress or uncontrolled symptoms, No. (%)	
Palliative medicine	9 (22.0)
Acute pain service	4 (9.8)
Psychiatry	10 (24.4)
Oral morphine equivalent dosage, mean (SD)[a]	
24-h total	75.3 (88.3)
As needed only	41 (32.3)
Antidepressants, No.(%)	23 (56.1)
Antipsychotics, No. (%)	6 (14.6)
Benzodiazepines, No. (%)	4 (9.8)
Muscle relaxants, No. (%)	5 (12.2)
Hypnotics, No. (%)	1 (2.4)
Stimulants, No. (%)	2 (4.9)
Anti-epileptic drugs/mood stabilizers, No. (%)	22 (53.7)
Gabapentin or pregabalin only	21 (51.2)
Adjuvant analgesics, all classes, No. (%)[a]	38 (92.7)
Acetaminophen	27 (65.9)
Gabapentin or pregabalin	21 (51.2)
Serotonin-norepinephrine reuptake inhibitor	8 (19.5)
Topical lidocaine	8 (19.5)
Muscle relaxant	5 (12.2)
Nonsteroidal anti-inflammatory, systemic	5 (12.2)
Other	9 (21.9)

[a]Totals may exceed 100%.

warehouse, which houses all barcode medication administration data collected at the point of care. The dataset includes pain scores gathered by nursing staff before and after administering an as-needed analgesic. The corporate data warehouse records data/time of pain scores and the analgesic name, dosage, formulation, and date/time of administration. Using a standardized assessment form developed iteratively, we calculated opioid dosage in oral morphine equivalents (OME) for comparison.[11,12] All abstracted data were reexamined for accuracy. Data initially were collected in an anonymized, blinded fashion. Participants were then unblinded for chart review. Initial data was captured in resident-days instead of unique residents because an individual resident might have been admitted on several observation days. We were primarily interested in how pain responded to opioids administered in response to resident request; therefore, we did not examine response to opioids that were continuously ordered (ie, scheduled). We did consider scheduled opioids when calculating total daily opioid dosage during the chart review.

Outcome of Interest

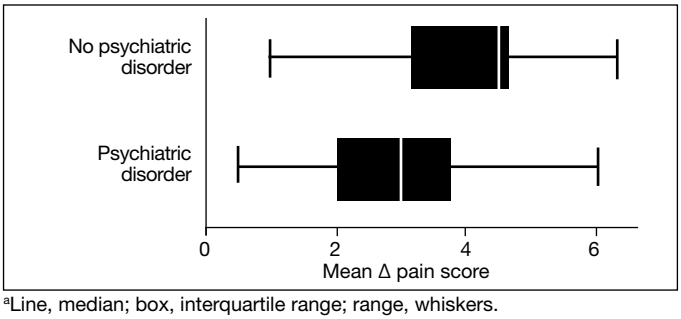
The primary outcome of interest was an individual's response to as-needed opioids, which we defined as change in the pain score after opioid administration. The preopioid pain score was the score that immediately preceded administration of an as-needed opioid. The postopioid administration pain score was the first score after opioid administration if obtained within

3 hours of administration. Scores collected > 3 hours after opioid administration were excluded because they no longer accurately reflected the impact of the opioid due to the short half-lives. Observations were excluded if an opioid was administered without a recorded pain score; this occurred once for 6 individuals. Observations also were excluded if an opioid was administered but the data were captured on the following day (outside of the 24-hour window); this occurred once for 3 individuals.

We calculated a Δ score by subtracting the postopioid pain rating score from the pre-opioid score. Individual Δ scores were then averaged over the 24-hour period (range, 2-5 opioid doses). For example, if an individual reported a pre-opioid pain score of 10, and a postopioid pain score of 2, the Δ was recorded as 8. If the individual's next pre-opioid score was 10, and postopioid score was 6, the Δ was recorded as 4. Δ scores over the 24-hour period were averaged together to determine that individual's response to as-needed opioids. In the previous example, the mean Δ score is 6. Lower mean Δ scores reflect decreased responsiveness to opioids' analgesic effect.

Demographic and clinical data were obtained from electronic health record review using a standardized assessment form. These data included information about medical and psychiatric comorbidities, specialist consultations, and CLC-PAC unit admission indications and diagnoses. Medications of interest were categorized as antidepressants, antipsychotics, benzodiazepines, muscle relaxants, hypnotics, stimulants, antiepileptic drugs/mood stabilizers (including gabapentin and pregabalin), and all adjuvant analgesics. Adjuvant analgesics were defined as medications administered for pain as documented by chart notes or those ordered as needed for pain, and analyzed as a composite variable. Antidepressants with analgesic properties (serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants) were considered adjuvant analgesics. Psychiatric information collected included presence of mood, anxiety, and psychotic disorders, and PTSD. SUD information was collected separately from other psychiatric disorders.

FIGURE 2 Psychiatric Disorder Associated With Reduced Opioid Responsiveness[a]



[a]Line, median; box, interquartile range; range, whiskers.

Analyses

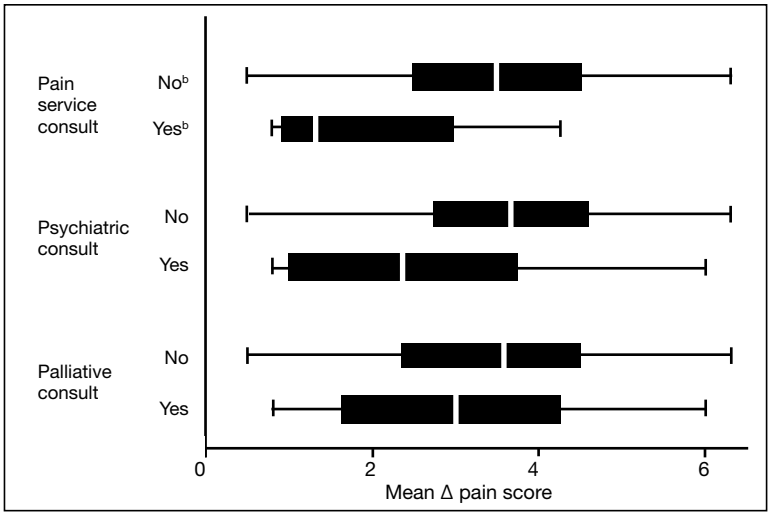
The study population was described using tabulations for categorical data and means and standard deviations for continuous data. Responsiveness to opioids was analyzed as a continuous variable. Those with higher mean Δ scores were considered to have pain relatively more responsive to opioids, while lower mean Δ scores indicated pain less responsive to opioids. We constructed linear regression models controlling for average pre-opioid pain rating scores to explore associations between opioid responsiveness and variables of interest. All analyses were completed using Stata version 15. This study was not adequately powered to detect differences across the spectrum of opioid responsiveness, although the authors have reported differences in this article.

RESULTS

Over the 4-day observational period there were 146 resident-days. Of these, 88 (60.3%) reported at least 1 pain score of ≥ 4. Of those, 61 (41.8%) received ≥ 1 as-needed opioid for pain. We identified 46 resident-days meeting study criteria of ≥ 2 pre- and postanalgesic scores. We identified 41 unique individuals (Figure 1). Two individuals were admitted to the CLC-PAC unit on 2 of the 4 observation days, and 1 individual was admitted to the CLC-PAC unit on 3 of the 4 observation days. For individuals admitted several days, we included data only from the initial observation day.

Response to opioids varied greatly in this sample. The mean (SD) Δ pain score was 3.4 (1.6) and ranged from 0.5 to 6.3. Using linear regression, we found no relationship between admission indication, medical comorbidities (including active cancer), and

FIGURE 3 Distress and Uncontrolled Symptoms Associated With Opioid Responsiveness[a]



[a]Line, median; box, interquartile range; range, whiskers.
[b]Statistically significant ($P < .05$).

opioid responsiveness (Table).

Psychiatric disorders were highly prevalent, with 25 individuals (61.0%) having ≥ 1 any psychiatric diagnosis identified on chart review. The presence of any psychiatric diagnosis was significantly associated with reduced responsiveness to opioids (β = –1.08; 95% CI, –2.04 to –0.13; $P = .03$). SUDs also were common, with 17 individuals (41.5%) having an active SUD; most were tobacco/nicotine. Twenty-six veterans (63.4%) had documentation of SUD in remission with 19 (46.3%) for substances other than tobacco/nicotine. There was no indication that any veteran in the sample was prescribed medication for opioid use disorder (OUD) at the time of observation. There was no relationship between opioid responsiveness and SUDs, neither active or in remission. Consults to other services that suggested distress or difficult-to-control symptoms also were frequent. Consults to the pain service were significantly associated with reduced responsiveness to opioids (β = –1.75; 95% CI, –3.33 to –0.17; $P = .03$). Association between psychiatry consultation and reduced opioid responsiveness trended toward significance (β = –0.95; 95% CI, –2.06 to 0.17; $P = .09$) (Figures 2 and 3). There was no significant association with palliative medicine consultation and opioid responsiveness.

A poorer response to opioids was associated with a significantly higher as-needed opioid dosage (β = –0.02; 95% CI, –0.04 to –0.01; $P = .002$) as well as a trend toward higher total opioid dosage (β = –0.005; 95% CI, –0.01 to 0.0003; $P = .06$) (Figure 4). Thirty-eight (92.7%) participants received nonopioid adjuvant analgesics for pain. More than half (56.1%) received antidepressants or gabapentinoids (51.2%), although we did not assess whether they were prescribed for pain or another indication. We did not identify a relationship between any specific psychoactive drug class and opioid responsiveness in this sample.

DISCUSSION

This exploratory study used readily available administrative data in a CLC-PAC unit to assess responsiveness to opioids via a numeric mean Δ score, with higher values indicating more pain relief in response to opioids. We then constructed linear regression models to characterize the relationship between the mean Δ score and factors known to be associated with difficult-to-control pain and psychosocial distress. As expected, opioid responsiveness was highly variable among residents; some residents experienced essentially no reduction in pain, on average, despite receiving opioids. Psychiatric comorbidity, higher dosage in OMEs, and the presence of a pain service consult significantly correlated with poorer response to opioids. To our knowledge, this is the first study to quantify opioid responsiveness and describe the relationship with clinical correlates in the understudied PAC population.

Earlier research has demonstrated a relationship between the presence of psychiatric disorders and increased likelihood of receiving any analgesics among veterans residing in PAC.[9] Our study adds to the literature by quantifying opioid response using readily available administrative data and examining associations with psychiatric diagnoses. These findings highlight the possibility that attempting to treat high levels of pain by escalating the opioid dosage in patients with a comorbid psychiatric diagnosis should be readdressed, particularly if there is no meaningful pain reduction at lower opioid dosages. Our sample had a variety of admission diagnoses and medical comorbidities, however, we did not identify a relationship with opioid

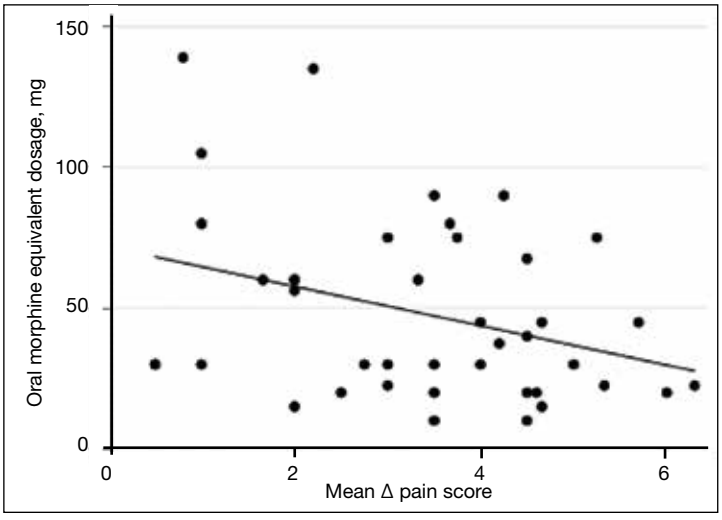
responsiveness, including an active cancer diagnosis. Although SUDs were highly prevalent in our sample, there was no relationship with opioid responsiveness. This suggests that lack of response to opioids is not merely a matter of drug tolerance or an indication of drug-seeking behavior.

Factors Impacting Response

Many factors could affect whether an individual obtains an adequate analgesic response to opioids or other pain medications, including variations in genes encoding opioid receptors and hepatic enzymes involved in drug metabolism and an individual's opioid exposure history.[13] The phenomenon of requiring more drug to produce the same relief after repeated exposures (ie, tolerance) is well known.[14] Opioid-induced hyperalgesia is a phenomenon whereby a patient's overall pain increases while receiving opioids, but each opioid dose might be perceived as beneficial.[15] Increasingly, psychosocial distress is an important factor in opioid response. Adverse selection is the process culminating in those with psychosocial distress and/or SUDs being prescribed more opioids for longer durations.[16] Our data suggests that this process could play a role in PAC settings. In addition, exaggerating pain to obtain additional opioids for nonmedical purposes, such as euphoria or relaxation, also is possible.[17]

When clinically assessing an individual whose pain is not well controlled despite escalating opioid dosages, prescribers must consider which of these factors likely is predominant. However, the first step of determining who has a poor opioid response is not straightforward. Directly asking patients is challenging; many individuals perceive opioids to be helpful while simultaneously reporting inadequately controlled pain.[7,8] The primary value of this study is the possibility of providing prescribers a quick, simple method of assessing a patient's response to opioids. Using this method, individuals who are responding poorly to opioids, including those who might exaggerate pain for secondary gain, could be identified. Health care professionals could consider revisiting pain management strategies, assess for the presence of OUD, or evaluate other contributors to inadequately controlled pain.

FIGURE 4 Relationship of Opioid Responsiveness With As-Needed Opioid Dose



Although we only collected data regarding response to opioids in this study, any pain medication administered as needed (ie, nonsteroidal anti-inflammatory drugs, acetaminophen) could be analyzed using this methodology, allowing identification of other helpful pain management strategies. We began the validation process with extensive chart review, but further validation is required before this method can be applied to routine clinical practice.

Patients who report uncontrolled pain despite receiving opioids are a clinically challenging population. The traditional strategy has been to escalate opioids, which is recommended by the World Health Organization stepladder approach for patients with cancer pain and limited life expectancy.[18] Applying this approach to a general population of patients with chronic pain is ineffective and dangerous.[19] The CDC and the VA/US Department of Defense (VA/DoD) guidelines both recommend carefully reassessing risks and benefits at total daily dosages > 50 OME and avoid increasing dosages to > 90 OME daily in most circumstances.[5,20] Our finding that participants taking higher dosages of opioids were not more likely to have better control over their pain supports this recommendation.

Limitations

This study has several limitations, the most significant is its small sample size because

of the exploratory nature of the project. Results are based on a small pilot sample enriched to include individuals with at least moderate pain who receive opioids frequently at 1 VA CLC-PAC unit; therefore, the results might not be representative of all veterans or a more general population. Our small sample size limits power to detect small differences. Data collected should be used to inform formal power calculations before subsequent larger studies to select adequate sample size. Validation studies, including samples from the same population using different dates, which reproduce findings are an important step. Moreover, we only had data on a single dimension of pain (intensity/severity), as measured by the pain scale, which nursing staff used to make a real-time clinical decision of whether to administer an as-needed opioid. Future studies should consider using pain measures that provide multidimensional assessment (ie, severity, functional interference) and/or were developed specifically for veterans, such as the Defense and Veterans Pain Rating Scale.[21]

Our study was cross-sectional in nature and addressed a single 24-hour period of data per participant. The years of data collection (2016 and 2017) followed a decline in overall opioid prescribing that has continued, likely influenced by CDC and VA/DoD guidelines.[22] It is unclear whether our observations are an accurate reflection of individuals' response over time or whether prescribing practices in PAC have shifted.

We did not consider the type of pain being treated or explore clinicians' reasons for prescribing opioids, therefore limiting our ability to know whether opioids were indicated. Information regarding OUD and other SUDs was limited to what was documented in the chart during the CLC-PAC unit admission. We did not have information on length of exposure to opioids. It is possible that opioid tolerance could play a role in reducing opioid responsiveness. However, simple tolerance would not be expected to explain robust correlations with psychiatric comorbidities. Also, simple tolerance would be expected to be overcome with higher opioid dosages, whereas our study demonstrates less responsiveness. These data suggests that some individuals' pain might be poorly opioid responsive, and psychiatric factors could increase this risk. We used a novel data source in combination with chart review; to our knowledge, barcode medication administration data have not been used in this manner previously. Future work needs to validate this method, using larger sample sizes and several clinical sites. Finally, we used regression models that controlled for average pre-opioid pain rating scores, which is only 1 covariate important for examining effects. Larger studies with adequate power should control for multiple covariates known to be associated with pain and opioid response.

CONCLUSIONS

Opioid responsiveness is important clinically yet challenging to assess. This pilot study identifies a way of classifying pain as relatively opioid nonresponsive using administrative data but requires further validation before considering scaling for more general use. The possibility that a substantial percentage of residents in a CLC-PAC unit could be receiving increasing dosages of opioids without adequate benefit justifies the need for more research and underscores the need for prescribers to assess individuals frequently for ongoing benefit of opioids regardless of diagnosis or mechanism of pain.

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Author affiliations

[a]Geriatric Research Education and Clinical Center, LTC Charles S. Kettles Veteran Affairs Medical Center, Ann Arbor, Michigan
[b]Division of Geriatric and Palliative Medicine, University of Michigan, Ann Arbor
[c]School of Nursing, University of Michigan, Ann Arbor

Author disclosures

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Ethics and consent

This study was approved by the institutional review board of the Ann Arbor VA Health System (#2017-1034).

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