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Short Communication

Are Opioids Agitating? A Data Analysis of Baseline Data from the STAN Study

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Abstract. Agitation, a common dementia symptom often arising from untreated pain, lacks comprehensive research on its connection with opioids prescribed for long-term pain. This study investigated the relationship between opioid use and agitation in dementia patients. Participants ($n = 188$) were categorized into opioid, acetaminophen PRN, or no-pain medication groups. Despite higher reported pain levels in the opioid group, no significant differences in agitation were observed among the groups. In conclusion, opioid use for pain management in older adults with dementia did not significantly impact agitation, emphasizing the ongoing importance of proper pain management in improving dementia care and addressing agitation in this population.

Keywords: Agitation, Alzheimer's disease, dementia, opioid, pain management

INTRODUCTION

Agitation is a common symptom associated with dementia, affecting up to 88% of patients with Alzheimer's disease and related dementias.[1] Agitation involves physical or verbal aggressiveness, exaggerated motor activity, and significant distress for the patient and others, and can significantly impact social relations, and daily activities.[2]

Agitation in dementia patients often stems from untreated pain, which is prevalent among seniors, especially in institutionalized settings.[3] Pain severity in this population may also be underestimated due to

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reliance on proxies for pain surveys, and communication difficulties can further hinder pain expression in this population.[4] While opioids are commonly prescribed for long-term pain in dementia, relatively limited research has explored their relationship with agitation.[5] Considering Canada's aging population, the high prevalence of chronic pain and the use of opioids among older adults with dementia, investigating the effectiveness and safety of opioid pharmacotherapy in managing agitation is crucial. Our study aims to compare the impact of opioid medication on agitation severity in older adults with dementia.

METHODS

This study was based on the baseline examination data from the Standardizing Care for Neuropsychiatric Symptoms and Quality of Life in Dementia (StaN) study. The original study took place in 9 sites across Canada. The study population consisted of patients aged $\geq$50 with a clinical diagnosis of Alzheimer's or dementia of mixed type and AD-AA as defined by Agitation in cognitive disorders.

Trained research analysts performed all assessments. Demographics, medical history, and current medication information were gathered. Cohen-Mansfield Agitation Inventory (CMAI) Total Frequency Score (CMAI-frequency), Total Disruptiveness Score (CMAI-disruptiveness) the agitation domain of the Neuropsychiatric Inventory-Clinician (NPI-C), and Pain Assessment in Advanced Dementia Scale (PAINAD) were conducted at baseline. Lastly, data on comorbidities that could affect opioid use were gathered.

Participants were divided into the opioid, acetaminophen PRN or no pain medication group. Those taking both acetaminophen and opioids were placed in the opioid group. Given that most of the participants were taking aspirin for cardiovascular conditions rather than for pain, acetylsalicylic acid was excluded from the list. Other topical NSAIDs were also excluded from the medication group.

CMAI-frequency scores between the opioid, acetaminophen PRN and no pain medication groups were analyzed using a one-way ANOVA to test the primary hypothesis. An ANCOVA assessed whether the CMAI frequency score-pain medication relationship was independent of PAINAD. Finally, a Spearman test was conducted to determine the correlation between pain and agitation scores. Statistical analysis was carried out with SPSS.[6]

RESULTS

A total of 188 participants in inpatient units ($n = 86$), long-term care facilities ($n = 67$), and other living arrangements ($n = 30$) were evaluated in this study. The mean age of the sample was 81 years old $\pm$ 9.5. Participants described their gender identity as male ($n = 90$), female ($n = 93$), and other ($n = 11$). Average C-MAI frequency scores were 56.54 ± 21.47, with a total score of >45 typically regarded as clinically significant agitation.[7] Average agitation NPI-C scores were 10.97 ± 7.60.

Patients were on a variety of medications for their health conditions. Pain medications were divided into three groups, Acetaminophen ($n = 84$), Opioid ($n = 16$), and Non-opioid ($n = 88$). Opioid medications used for pain include fentanyl, hydromorphone, oxycodone, codeine, and buprenorphine. No patients were using methadone.

Average PAINAD scores were 1.11 ± 1.79. The Opioid group ($n = 11$, 3.55 ± 2.77) reported significantly higher ($p < 0.001$) pain compared to the Acetaminophen ($n = 52$, 0.62 ± 1.33) and Non-opioid group ($n = 54$, 1.09 ± 1.53). The results of a one-way ANOVA showed no significant differences in CMAI-frequency scores ($p = 0.734$) between the Acetaminophen ($n = 84$, 57.86 ± 23.89), Opioid ($n = 16$, 54.63 ± 16.08) and non-opioid group ($n = 88$, 55.64 ± 19.95). Post-hoc analyses using Tukey's honestly significant difference (HSD) test were conducted to determine the specific group differences, and no significant differences were found in CMAI frequency scores between the acetaminophen group, opioid or nonopioid groups ($p = 0.805$). Similarly, no differences in CMAI frequency scores were observed when controlling for pain ($p = 0.258$) between the three groups. A significantly positive correlation was observed between CMAI frequency and PAINAD scores (Correlation 0.150, Spearman's rho 0.211, $p < 0{,}05$).

No differences were found in CMAI-frequency or PAINAD scores between participants in inpatient or long-term care settings.

DISCUSSION

We examined data from 188 participants from a large real-world, pragmatic, multi-site, Canadian randomized control trial to examine the relationship between pain medication use and agitation scores in older adults with dementia. Our sample had a

low prevalence of opioid use (8.51%), as compared to 16.3% of Canadian long-term care (LTC) residents with dementia and 26% of residents without dementia.[8] Pain levels were higher among opioid users and were correlated with increased agitation. However, our main result did not find a significant relationship between opioid use and agitation scores, even when controlling for concurrent pain.

Previous studies have found inappropriate opioid prescribing in older adults to be associated with increased mortality, psychosis, falls, and memory problems,[9] and a recent cohort study reported that inappropriate opioid prescribing in two areas of pain care was more common among patients with Alzheimer's disease and related dementia than those without dementia in community and LTCH settings.[10]

However, our study's findings are consistent with that of recent large RCTs on pain and dementia, which have found that pain management significantly reduces agitation[11,2] and that the use of opioids did not increase psychotic symptoms.[12] Older patients experience more chronic pain than the general population, characterized by poor localization and longer duration.[12] Chronic pain, combined with advanced dementia, leads to difficulties verbally expressing pain, resulting in aggressive and agitated behaviours. Low-dose, long-acting opioids have been shown to decrease agitation scores in older patients with advanced dementia.[14]

The present study had notable strengths, including its large scale, involving multiple sites in two settings, encompassing various inpatient units and long-term care facilities. The data collected provided valuable insights into real-world medication use and highlighted the prevalence of agitation in this demographic. However, there were limitations, such as a relatively small sample of patients using opioids and the absence of a control group of non-agitated patients. We were also unable to do subgroup analyses according to participant characteristics such as frailty. Future studies with larger samples of opioid users and the inclusion of control groups would enhance our understanding of the relationship between pain and agitation in this population.

Conclusion

Our study suggests that the appropriate use of opioids to manage pain is not associated with increased agitation. Considering the high prevalence of chronic pain among older patients, especially those with advanced dementia, adequately addressing pain remains crucial in managing agitation and improving the quality of dementia care. Further research, including additional large real-world cohort studies and randomized control trials, is necessary to gain a comprehensive understanding of the short- and long-term effects of opioid use on agitation in older adults living with dementia.

AUTHOR CONTRIBUTIONS

Myriam Lesage (Formal analysis; Writing – original draft; Writing – review & editing); Karin Cinalioglu (Writing – original draft); Sabrina Chan Chun Kong (Formal analysis; Writing – review & editing); Sanjeev Kumar (Conceptualization; Funding acquisition; Investigation; Writing – review & editing); Tarek Rajji (Conceptualization; Funding acquisition); Ashley Melichercik (Project administration; Writing – review & editing); Carmen Desjardins (Validation); Jess Friedland (Validation); Amer Burhan (Conceptualization; Funding acquisition); Sarah Colman (Conceptualization; Funding acquisition); Li Chu (Conceptualization; Funding acquisition); Simon Davies (Conceptualization; Funding acquisition); Peter Derkach (Conceptualization; Funding acquisition); Sarah Elmi (Funding acquisition); Philip Gerretsen (Conceptualization; Funding acquisition); Ariel Graff-Guerrero (Conceptualization; Funding acquisition); Maria Hussain (Conceptualization; Funding acquisition); Zahinoor Ismail (Conceptualization; Funding acquisition); Rola Moghabghab (Conceptualization; Funding acquisition); Benoit H. Mulsant (Conceptualization; Funding acquisition); Bruce G. Pollock (Conceptualization; Funding acquisition); Aviva Rostas (Conceptualization; Funding acquisition); Lisa Van Bussel (Conceptualization; Funding acquisition); Soham Rej (Conceptualization; Formal analysis; Supervision; Validation; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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