Drugs & Aging (2025) 42:267–274
https://doi.org/10.1007/s40266-025-01181-w

ORIGINAL RESEARCH ARTICLE

Dementia Medications and Their Association with Pain Medication Use in Medicare Beneficiaries with Alzheimer's Disease/Alzheimer's Disease-Related Dementias and Chronic Pain

Sadaf Arefi Milani[1] · Jordan Westra[1] · Yong-Fang Kuo[2] · Brian Downer[3] · Mukaila A. Raji[4]

Accepted: 12 January 2025 / Published online: 26 February 2025

Abstract

Introduction Chronic pain is prevalent among older adults with Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD). Memantine and acetylcholinesterase inhibitors (ACHEI; donepezil, rivastigmine, and galantamine) are approved for the treatment of dementia symptoms and may also have analgesic properties. However, findings on the clinical utility of these dementia medications for chronic pain treatment are mixed, and little is known about differences in the use of pain medication according to whether an older adult with AD/ADRD is using dementia medications.

Methods We selected a 20% national sample of Medicare enrollees with a diagnosis of AD/ADRD and chronic pain in 2020. We calculated the odds of having any pain management prescription (opioids, serotonin and norepinephrine reuptake, gapapentinoids, or non-steroidal anti-inflammatory drugs), having an opioid prescription, and having a long-term (≥ 90 days) opioid prescription, by dementia medication (none, memantine, ACHEI, or memantine and ACHEI).

Results Among 103,564 patients, 5.5% received a memantine prescription, 14.4% received an ACHEI prescription, and 8.6% received a prescription for both. Over 70% of all patients had a pain management prescription. The percentage of patients who had an opioid prescription ranged from 54.5% for those without a dementia medication prescription to 44.0% for those with a prescription for both memantine and ACHEI. Similarly, the percentage of patients who had a long-term opioid prescription was highest for those without a dementia medication prescription (12.2%) and lowest for those with a prescription for both memantine and ACHEI (8.8%). Having a prescription for memantine only was associated with lower odds of any pain management prescription (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.88–1.00; $p < 0.05$). Having a prescription for either memantine (OR: 0.79; 95% CI 0.75–0.84), ACHEI (OR: 0.85; 95% CI 0.82–0.89), or both (OR: 0.75; 95% CI 0.72–0.79) was associated with lower odds of having an opioid prescription ($p < 0.05$). Lastly, having a prescription for either memantine (OR: 0.85; 95% CI 0.77–0.94), ACHEI (OR: 0.92; 95% CI 0.86–0.98), or both (OR: 0.83; 95% CI 0.77–0.90) was associated with lower odds of having a long-term opioid prescription.

Discussion Older adults with co-occurring AD/ADRD and chronic pain who were on dementia medications had lower odds of being prescribed opioid analgesics. Memantine and ACHEIs should be explored as potential opioid-sparing medications for older adults with AD/ADRD, given their relatively safe profiles. Future studies are needed to examine repurposing dementia medications for pain treatment.

1 Introduction

In 2024, almost seven million Americans, or one in nine adults aged 65 years and older, were living with Alzheimer's dementia [1]. Chronic pain is common among those with Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) [2]. Estimates of chronic pain prevalence range from 50% of community-dwelling individuals with AD/ADRD to 60–80% of nursing home residents with AD/ADRD [3, 4]. Despite the high prevalence of pain among them, no pain management guidelines exist for older adults with AD/ADRD [2].

Memantine and acetylcholinesterase inhibitors (ACHEIs) are approved for the treatment of AD/ADRD symptoms [5]. Recent work has suggested that these medications also have analgesic properties [6, 7]. Memantine, a *N*-methyl-D-aspartate (NMDA) antagonist, may have the potential to modify pain signals, given the role that NMDA receptors play in the generation and continuation of pain signals [6]. However, findings are mixed on whether memantine can reduce

Extended author information available on the last page of the article

Key Points

In our study of Medicare beneficiaries with AD/ADRD and chronic pain, we found that memantine and/or ACHEI prescriptions were associated with lower odds of having any opioid prescription and a long-term opioid prescription.

Memantine and ACHEIs may be potential opioid-sparing medications for older adults with AD/ADRD and chronic pain, but future studies are needed to understand the temporality in the association between memantine and/or ACHEI prescribing and opioid prescribing.

pain [8]. A recent systematic review of 15 studies [8] found evidence that memantine can reduce fibromyalgia pain [9, 10], neuropathic pain [11], or postoperative pain [12, 13]. However, these experimental studies focused on specific pain conditions, rather than chronic pain in general, and had sample sizes of less than 100. The effects of ACHEIs on pain are less widely studied, but share a similar mechanism through which pain mechanisms are subject to cholinergic modulation and may improve chronic pain [7].

A large-scale study is needed to understand whether memantine and ACHEIs are associated with pain medication prescribing. Our objective was to assess the association of dementia medications with patterns of pain medication prescriptions among Medicare beneficiaries with a diagnosis of AD/ADRD and chronic pain in 2020. We hypothesize that dementia medications will be associated with lower odds of prescription of any pain medications, including opioids and long-term opioid prescriptions.

2 Methods

2.1 Data Source

We used a 20% national sample of Medicare enrollees with a diagnosis of AD/ADRD and chronic pain in 2020 based on algorithms from the Chronic Conditions Data Warehouse (CCW) [14, 15]. We used the Master Beneficiary Summary File, Medicare Provider Analysis and Review file, Outpatient Standard Analytic File, Carrier, and Prescription Drug Event files. We included those with continuous Part A, B, and D enrollment from 2018 to 2020 and complete demographic information. AD/ADRD diagnosis required a 3-year reference period [14]. We operationalized chronic pain using the algorithm from the CCW, requiring one inpatient claim or two other nondrug claims that were at least 1 day apart over a 2-year reference period [15]. Our study was approved by the University of Texas Medical Branch Institutional Review Board (IRB: 16-0247).

2.2 Measures

Our exposure was the prescription of dementia medications in 2020, specifically memantine and ACHEIs. This was categorized as a four-level variable: none, memantine only, ACHEI only, or both memantine and ACHEI. Our main outcome included prescription pain medications. These included prescription opioids, serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine), gabapentinoids (gabapentin and pregabalin), and non-steroidal anti-inflammatory drugs. We examined (1) having any pain management prescription; (2) having any opioid prescription; and (3) having a long-term opioid prescription, defined as at least 90 days of consecutive opioid prescriptions in 2020. We identified prescription opioids according to the National Drug Code (complete, partial, and combination opioid agonists were included). Therapeutic classes of prescription medications included in our analyses are included in Supplementary Table 1.

Covariates included age, sex, race and ethnicity, region, original entitlement (disability/end stage renal disease, old age), dual Medicaid coverage, chronic conditions, mental health conditions, opioid use disorder, drug or alcohol abuse, and pain type/location. Chronic conditions included were cancer, hypertension, heart failure, ischemic heart disease, arrhythmia, hyperlipidemia, stroke/transient ischemic attack (TIA), arthritis, asthma, autism, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), liver disease, osteoporosis, and schizophrenia. There was a total of 17 conditions used, and all but arrhythmia were from the CCW [16]. Arrhythmia used an International Classification of Diseases, Tenth Revision (ICD-10) code of I48.x. Cancer included any breast, colorectal, prostate, lung, endometrial, and leukemia/lymphoma cancer diagnosis, but only counted as one condition. Chronic conditions were summed from 0 to 17. Mental health conditions included depression, bipolar disorder, and anxiety. Pain type/locations included back pain, neck pain, headaches, general chronic pain, abdominal/chest pain, cancer, musculoskelal pain, fractures, visceral pain, wound pain, and other pain. A list of ICD codes used to identify pain type/location is detailed in Supplementary Table 2.

2.3 Statistical Analysis

We used logistic regression models to assess the odds of (1) having any pain management prescription, (2) having an opioid prescription, and (3) having a long-term (≥ 90 days) opioid prescription, by dementia medication group. We controlled for age, sex, race and ethnicity, region, original entitlement, dual Medicaid coverage, chronic conditions count, mental health conditions (depression, anxiety, and bipolar), opioid use disorder, drug or alcohol abuse, and pain type/location. We conducted sensitivity analyses where we (1) analyzed the three classes of ACHEIs separately and (2) excluded those with cancer. All analysis was conducted with SAS Enterprise Guide 7.1 (SAS Inc., Cary, NC) .

3 Results

Our cohort included 103,564 patients, who were mostly female and non-Hispanic white. Table 1 displays our sample characteristics by dementia medication group. Of these individuals, 5.5% received a memantine prescription, 14.4% received an ACHEI prescription, and 8.6% received a prescription for both. Over 70% of all patients had a pain management prescription. The percentage of patients who had an opioid prescription ranged from 54.5% for those without a dementia medication prescription to 44.0% for those with a prescription for both memantine and ACHEI. Similarly, the percentage of patients who had a long-term opioid prescription was highest for those without a dementia medication prescription (12.2%) and lowest for those with a prescription for both memantine and ACHEI (8.8%).

We also noted differences in AD/ADRD medication prescribing by demographic group. For instance, those without a AD/ADRD prescription were more often non-Hispanic Black (8.8%) compared with those with a memantine prescription (6.3%), ACHEI prescription (7.1%), or both (6.2%). Alternatively, those with no AD/ADRD prescriptions were less often Hispanic (5.4%) compared with those with a memantine prescription (7.7%), ACHEI prescription (6.0%), or both (6.7%). The two most common pain locations were back pain and abdominal/chest pain, with minor differences in frequency of memantine and/or ACHEI prescribing: 43.6% of patients who did not have any dementia prescriptions had a diagnosis of back pain compared with 43.0% with a memantine prescription, 44.1% with an ACHEI prescription, and 43.3% with a prescription for both AD/ADRD drugs. There were also some differences in the frequency of AD/ADRD prescribing in patients with abdominal/chest pain: 36.1% of patients who did not have any dementia prescriptions had a diagnosis of abdominal/chest pain compared with 32.3% with a memantine prescription, 30.8% with an ACHEI prescription, and 28.0% with a prescription for both AD/ADRD drugs.

In adjusted analyses, having a prescription for memantine only was associated with lower odds of having any pain management prescription (odds ratio [OR]: 0.94; 95% confidence interval [CI]: 0.88–1.00; $p < 0.05$; Fig. 1; Supplementary Table 3). Having a prescription for either memantine (OR: 0.79; 95% CI 0.75–0.84), ACHEI (OR: 0.85; 95% CI 0.82–0.89), or both (OR: 0.75; 95% CI 0.72–0.79) was associated with lower odds of having an opioid prescription ($p < 0.05$). Lastly, having a prescription for either memantine (OR: 0.85; 95% CI 0.77–0.94), ACHEI (OR: 0.92; 95% CI 0.86–0.98), or both (OR: 0.83; 95% CI 0.77–0.90) was associated with lower odds of having a long-term opioid prescription.

In a supplementary analysis that separated ACHEIs by class, the most commonly prescribed ACHEI was donepezil (Supplementary Table 4). In adjusted analyses, we found that no AD/ADRD medications were associated with odds of having any prescription pain management (Supplementary Table 5). Memantine, donepezil, donepezil and memantine, galamantine and memantine, rivastigmine, and rivastigmine and memantine were all associated with lower odds of opioid prescription. Additionally, memantine, donepezil, donepezil and memantine, galamantine and memantine, and rivastigmine and memantine were all associated with lower odds of having a long-term opioid prescription. Lastly, when we excluded those with cancer, our findings were consistent with our main results. We found that AD/ADRD medications were not associated with any pain management prescription, but memantine only, ACHEI only, and memantine and ACHEI were associated with lower odds of both opioid prescription and 90-day opioid prescription.

4 Discussion

In our study of Medicare beneficiaries with AD/ADRD and chronic pain, we found that memantine and/or ACHEI prescriptions were associated with lower odds of having any opioid prescription and a long-term opioid prescription. Additionally, a memantine prescription was associated with lower odds of having any pain medication prescription. Our findings suggest that these dementia medications could be potential opioid-sparing medications and could contribute to deprescribing efforts and reduction of polypharmacy among older adults with AD/ADRD. These two medication classes are good candidates for drug-repurposing, as they are Food and Drug Administration (FDA)-approved, well studied, and relatively inexpensive. However, more research is needed to

Table 1 Beneficiary characteristics by AD/ADRD medication group ($n = 103,564$)

	None ($n = 74,009$; 71.5%)		Memantine only ($n = 5679$; 5.5%)		ACHEI only ($n = 14,942$; 14.4%)		Memantine + ACHEI ($n = 8934$; 8.6%)	
	N	%	*N*	%	*N*	%	*N*	%
Age, years								
Mean, SD	78.3	11.3	80.6	8.6	80.4	8.3	80.5	7.6
≤ 65	8247	11.1%	252	4.4%	581	3.9%	271	3.0%
66–70	7142	9.7%	362	6.4%	1048	7.0%	568	6.4%
71–75	12,186	16.5%	815	14.4%	2281	15.3%	1309	14.7%
76–80	13,121	17.7%	1199	21.1%	3353	22.4%	2155	24.1%
81–85	12,710	17.2%	1338	23.6%	3533	23.6%	2266	25.4%
≥ 86	20,603	27.8%	1713	30.2%	4146	27.7%	2365	26.5%
Sex								
Male	23,945	32.4%	1774	31.2%	4983	33.3%	2966	33.2%
Female	50,064	67.6%	3905	68.8%	9959	66.7%	5968	66.8%
Race								
White	60,277	81.4%	4576	80.6%	12,249	82.0%	7367	82.5%
Black	6513	8.8%	356	6.3%	1061	7.1%	552	6.2%
Other	1520	2.1%	141	2.5%	289	1.9%	179	2.0%
Asian	1723	2.3%	170	3.0%	443	3.0%	240	2.7%
Hispanic	3976	5.4%	436	7.7%	900	6.0%	596	6.7%
Region								
Midwest	16,734	22.6%	1194	21.0%	3321	22.2%	1891	21.2%
Northeast	13,955	18.9%	908	16.0%	2408	16.1%	1316	14.7%
South	29,651	40.1%	24	0.4%	6476	43.3%	4194	46.9%
West	13,669	18.5%	1129	19.9%	2737	18.3%	1533	17.2%
Original entitlement								
Disability/ESRD	22,122	29.9%	1213	21.4%	3163	21.2%	1705	19.1%
Old age	51,887	70.1%	4466	78.6%	11,779	78.8%	7229	80.9%
Medicaid dual eligibility								
No	43,541	58.8%	3258	57.4%	9782	65.5%	5637	63.1%
Yes	30,468	41.2%	2421	42.6%	5160	34.5%	3297	36.9%
Rural/urban								
Metro	59,278	80.1%	4591	80.8%	11,685	78.2%	7085	79.3%
Non-metro urban	11,014	14.9%	807	14.2%	2406	16.1%	1367	15.3%
Rural	3717	5.0%	281	4.9%	851	5.7%	482	5.4%
Chronic conditions (max. 17)								
Mean, SD	5.5	2.4	5.2	2.3	5.1	2.3	4.9	2.3
0–2	8740	11.8%	709	12.5%	2183	14.6%	1372	15.4%
3	7647	10.3%	666	11.7%	1853	12.4%	1250	14.0%
4	9598	13.0%	846	14.9%	2234	15.0%	1395	15.6%
5	10,825	14.6%	910	16.0%	2361	15.8%	1443	16.2%
6	11,141	15.1%	850	15.0%	2126	14.2%	1242	13.9%
7	10,193	13.8%	711	12.5%	1766	11.8%	986	11.0%
8	7941	10.7%	507	8.9%	1280	8.6%	671	7.5%
≥ 9	7924	10.7%	480	8.5%	1139	7.6%	575	6.4%
Depression	40,496	54.7%	3325	58.5%	8284	55.4%	5128	57.4%
Bipolar disorder	9545	12.9%	694	12.2%	1554	10.4%	990	11.1%
Anxiety	38,080	51.5%	2914	51.3%	7091	47.5%	4214	47.2%
Opioid use disorder	8173	11.0%	367	6.5%	950	6.4%	494	5.5%

Table 1 (continued)

	None (n = 74,009; 71.5%)		Memantine only (n = 5679; 5.5%)		ACHEI only (n = 14,942; 14.4%)		Memantine + ACHEI (n = 8934; 8.6%)	
	N	%	*N*	%	*N*	%	*N*	%
Drug use	9707	13.1%	483	8.5%	1176	7.9%	617	6.9%
Alcohol abuse	4241	5.7%	196	3.5%	451	3.0%	236	2.6%
Pain type/location								
Back pain	32,279	43.6%	2440	43.0%	6586	44.1%	3868	43.3%
Nerve pain	9186	12.4%	648	11.4%	1656	11.1%	953	10.7%
Headaches	9079	12.3%	701	12.3%	1703	11.4%	966	10.8%
General chronic pain	15,049	20.3%	996	17.5%	2479	16.6%	1449	16.2%
Abdominal/chest pain	26,719	36.1%	1836	32.3%	4606	30.8%	2500	28.0%
Cancer	11,845	16.0%	824	14.5%	2249	15.1%	1219	13.6%
Musculoskeletal pain	10,373	14.0%	672	11.8%	1784	11.9%	1047	11.7%
Fractures	14,733	19.9%	977	17.2%	2501	16.7%	1357	15.2%
Visceral pain	7634	10.3%	461	8.1%	1259	8.4%	636	7.1%
Wound pain	9715	13.1%	715	12.6%	1789	12.0%	1008	11.3%
Other pain	11,653	15.7%	801	14.1%	2028	13.6%	1115	12.5%
Pain management								
Any prescription for pain	56,226	76.0%	4154	73.1%	10,970	73.4%	6448	72.2%
Opioid prescription	40,303	54.5%	2648	46.6%	7099	47.5%	3932	44.0%
90-day opioid prescription	9013	12.2%	528	9.3%	1454	9.7%	784	8.8%

Chronic conditions included were cancer, hypertension, heart failure, ischemic heart disease, arrhythmia, hyperlipidemia, stroke/TIA, arthritis, asthma, autism, CKD, COPD, diabetes, HIV/AIDS, liver disease, osteoporosis, and schizophrenia. There was a total of 17 conditions used, and all but arrhythmia are from the Chronic Conditions Data Warehouse. Arrhythmia used an ICD-10 code of I48.x. Cancer included any breast, colorectal, prostate, lung, endometrial, and leukemia/lymphoma cancer diagnosis but only counted as one condition. *ESRD* end-stage renal disease; *SD* standard deviation

determine their clinical utility in treating pain among older adults with AD/ADRD.

While both memantine and ACHEI are associated with lower odds of prescription opioid use, only memantine was associated with lower odds of having a prescription for any pain management. The evidence for the analgesic effects of ACHEIs is limited compared with memantine, but some studies have found that neostigmine (commonly used for myasthenia gravis) may be one ACHEI that is effective in managing pain [7]. However, this has not been examined in a large population of patients with AD/ADRD. Future work is needed to disentangle the analgesic effects of these two drugs and consider dementia severity, how long patients have been living with AD/ADRD and chronic pain diagnoses, and the temporality and dosage of medications.

There may also be potential differences in the analgesic potential of the three FDA-approved ACHEIs, given some differences in their mechanism of action beyond ACHEI. For example, galantamine—the only ACHEI with modulating effects on nicotinic acetylcholine receptors—has been shown to have potential anti-arthritis and analgesic effects [17, 18]. Likewise, rivastigmine, which also inhibits butyryl cholinesterase, has been associated with suppression of inflammatory markers—which play key roles in nociceptive pain [19]. In the context of data showing an overall decrease in the prescription of AD drugs [20], the findings for these drugs to have potential analgesic effects—if confirmed in larger longitudinal studies with a new-user active-comparator design—can guide shared therapeutic decision-making discussion between patients, their care partners, and clinicians.

Overall, we documented low prescribing of AD/ADRD medications. Our finding that only 28.5% of patients living with AD/ADRD and chronic pain are prescribed memantine and/or ACHEI is comparable to prior research that found that 33.3% of Medicare beneficiaries diagnosed with AD/ADRD used either an ACHEI or memantine during their study period (2008–2016) [21]. This is perhaps a reflection at least in part of modest and short-term beneficial effects of these drugs on cognition and function in patients with AD/ADRD and the unclear clinical guideline on when to start, stop, or continue these drugs [22–24]. For most of the pain locations, memantine and ACHEIs were less often prescribed. The reasons for this are unclear, but prescribers may be hesitant to initiate AD/ADRD medications for patients with abdominal/chest pain, given the potential

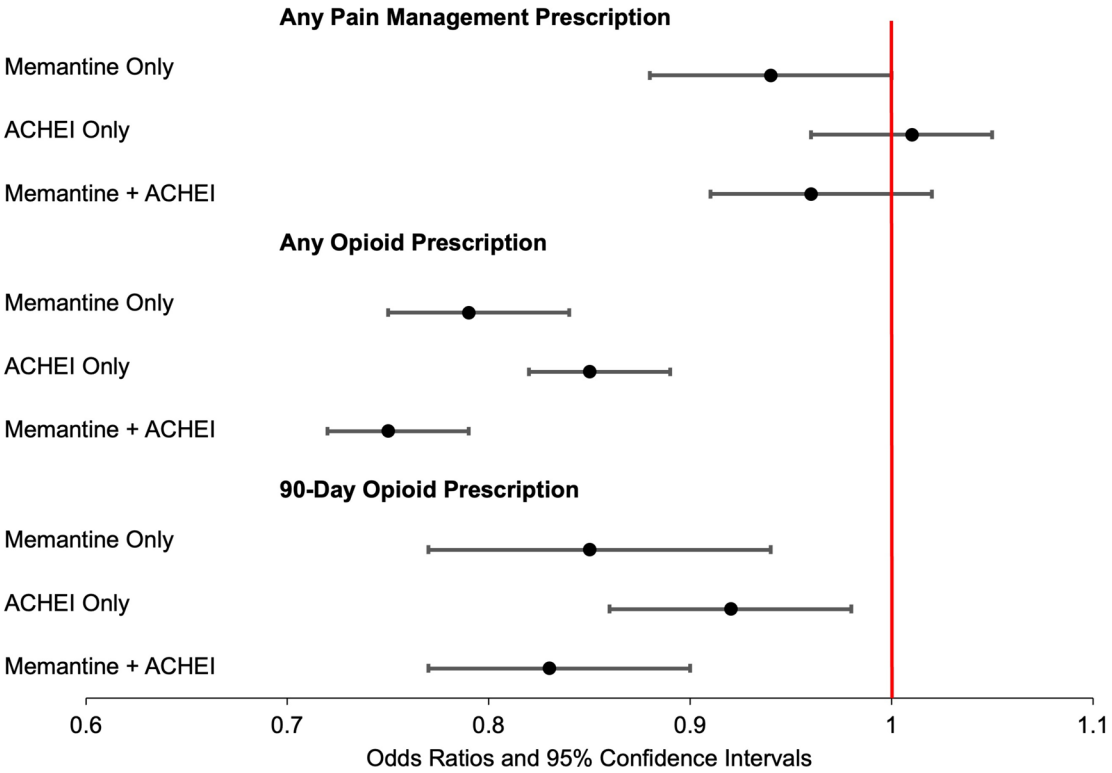

Fig. 1 Odds of having an opioid prescription, by dementia medication use (reference group: no dementia medication; $n = 103{,}564$)

gastrointestinal side effects, especially with the ACHEI drugs [25, 26].

While opioid medications are commonly used for chronic pain, the revised 2022 Centers for Disease Control and Prevention Clinical Practical Guideline for Prescribing Opioids for Pain recommends that opioid medications not be used as first-line analgesics for patients with chronic pain [27]. Yet, ensuring proper pain control can help with neuropsychiatric symptoms among those with dementia, such as aggression or agitation [28]. Second, drug repositioning is a growing priority with many advantages, such as a simiplified regulatory approval, and faster development [29]. Repositioning AD/ADRD medications to address pain may help reduce polypharmacy among older adults with AD/ADRD. Last, we noted racial and ethnic differences in the prescribing of AD/ADRD medications, which is consistent with prior work [21]. We found that the highest proportion of those without a prescription for memantine and/or ACHEIs comprised of non-Hispanic Black beneficiaries, while Hispanic beneficiaries composed the lowest proportion of patients without any AD/ADRD prescription. This highlights a need to address these prescription disparities and understand whether these reflect patient preferences for treatment.

A limitation of our analysis is that we did not consider how long patients were diagnosed with AD/ADRD or chronic pain or how long they had been prescribed dementia medications or opioid medications prior to inclusion in the study. We also did not investigate dosage or duration of prescriptions for AD/ADRD. In addition, pain is likely underdiagnosed and undertreated among those with AD/ADRD. Future work is needed to examine changes in pain before and after taking AD/ADRD medications to understand whether these medications truly have analgesic effects or whether this is an artifact of the undertreating of pain. We will address these in future studies. Additionally, our work reflects prescriptions filled, not their use, and we did not have information on the severity of AD/ADRD; however, these are a limitations applicable to all studies using claims data. Lastly, Medicare records may not have accurate diagnoses, but prior work has found that dementia diagnosis claims in Medicare data had a sensitivity of 85% and a specificity of 87% [30].

4.1 Conclusions

Our study suggests that patients with AD/ADRD and chronic pain who are prescribed memantine and/or ACHEIs have lower odds of being prescribed opioids. This is a first step toward understanding the association of dementia medication with potential analgesic effects among individuals living with AD/ADRD and chronic pain. Future work is warranted to consider temporality in the prescribing of these medications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-025-01181-w.

Declarations

Funding This work was supported by the National Institute on Aging (NIA)/National Institutes of Health (NIH) (grant nos. K01-AG075254, P30-AG024832, P30-AG059301) and the National Institute on Drug Abuse (grant no. R01-DA039192). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no involvement in the study design, analysis, interpretation, writing of the manuscript, or decision to submit this article for publication.

Conflicts of Interest S.A.M., J.W., Y.F.K., B.D., and M.R. declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval Our use of the 20% National Medicare data was approved by the University of Texas Medical Branch Institutional Review Board (16-0247).

Consent Not applicable.

Data Availability Statement The data used in this study are not publically available and require a data use agreement (DUA) from the Centers for Medicare & Medicaid Services.

Code Availability Not applicable.

Author Contributions S.A.M., Y.F.K., and M.R. were involved in the conceptualization, design, interpretation of the results, and editing of the manuscript. B.D. contributed to the interpretation of the results and editing of the manuscript. J.W. conducted data analysis. All authors edited and approved the final version of the manuscript.

References

1. Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708–821. https://doi.org/10.1002/alz.13809.
2. Achterberg W, Lautenbacher S, Husebo B, Erdal A, Herr K. Pain in dementia. Pain Rep. 2020;5(1): e803.
3. Corbett A, Husebo B, Malcangio M, Staniland A, Cohen-Mansfield J, Aarsland D, Ballard C. Assessment and treatment of pain in people with dementia. Nat Rev Neurol. 2012;8(5):264–74.
4. Barry HE, Parsons C, Passmore AP, Hughes CM. Exploring the prevalence of and factors associated with pain: a cross-sectional study of community-dwelling people with dementia. Health Soc Care Comm. 2016;24(3):270–82.
5. Reuben DB, Kremen S, Maust DT. Dementia prevention and treatment: a narrative review. JAMA Intern Med. 2024;184(5):563–72.
6. Shanthanna H. Chapter 13—memantine: features and application in the management of chronic pain. In: Rajendram R, Patel VB, Preedy VR, Martin CR, editors. Treatments, mechanisms, and adverse reactions of anesthetics and analgesics. Academic Press; 2022. p. 121–30.
7. Eldufani J, Blaise G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: a review of recent clinical applications. Alzheimers Dement (NY). 2019;5:175–83.
8. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. Euro J Pain. 2019;23(7):1234–50.
9. Olivan-Blázquez B, Herrera-Mercadal P, Puebla-Guedea M, Pérez-Yus MC, Andrés E, Fayed N, et al. Efficacy of memantine in the treatment of fibromyalgia: a double-blind, randomised, controlled trial with 6-month follow-up. Pain. 2014;155(12):2517–25.
10. Fayed N, Olivan-Blázquez B, Herrera-Mercadal P, Puebla-Guedea M, Pérez-Yus MC, Andrés E, et al. Changes in metabolites after treatment with memantine in fibromyalgia. A double-blind randomized controlled trial with magnetic resonance spectroscopy with a 6-month follow-up. CNS Neurosci Ther. 2014;20(11):999–1007.
11. Gustin SM, Schwarz A, Birbaumer N, Sines N, Schmidt AC, Veit R, et al. NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. Pain. 2010;151(1):69–76.
12. Morel V, Etienne M, Wattiez AS, Dupuis A, Privat AM, Chalus M, et al. Memantine, a promising drug for the prevention of neuropathic pain in rat. Eur J Pharmacol. 2013;721(1–3):382–90.
13. Schley M, Topfner S, Wiech K, Schaller HE, Konrad CJ, Schmelz M, Birbaumer N. Continuous brachial plexus blockade in combination with the NMDA receptor antagonist memantine prevents phantom pain in acute traumatic upper limb amputees. Eur J Pain. 2007;11(3):299–308.
14. Chronic Conditions Data Warehouse. Alzheimer's disease, related disorders, or senile dementia. Available from: https://www2.ccwdata.org/web/guest/condition-categories. Accessed 11 Dec 2024.
15. Chronic Conditions Data Warehouse. Fibromyalgia, chronic pain and fatigue Available from: https://www2.ccwdata.org/web/guest/condition-categories. Accessed 11 Dec 2024.
16. Chronic Conditions Data Warehouse. Chronic conditions. Available from: https://www2.ccwdata.org/web/guest/condition-categories-chronic#cc27. December 11, 2024.
17. Gowayed MA, Rothe K, Rossol M, Attia AS, Wagner U, Baerwald C, et al. The role of α7nAChR in controlling the anti-inflammatory/anti-arthritic action of galantamine. Biochem Pharmacol. 2019;170: 113665.
18. Gowayed MA, Mahmoud SA, Michel TN, Kamel MA, El-Tahan RA. Galantamine in rheumatoid arthritis: a cross talk of

parasympathetic and sympathetic system regulates synovium-derived microRNAs and related pathogenic pathways. Eur J Pharmacol. 2020;883: 173315.
19. Nizri E, Irony-Tur-Sinai M, Faranesh N, Lavon I, Lavi E, Weinstock M, Brenner T. Suppression of neuroinflammation and immunomodulation by the acetylcholinesterase inhibitor rivastigmine. J Neuroimmunol. 2008;203(1):12–22.
20. Ben Hassen C, Tahir R, Singh-Manoux A, Milic D, Paquet C, Sabia S, Dumurgier J. Ten-year trends in sales of Alzheimer disease drugs in France compared with sales in Germany, Spain, and the UK. JAMA Health Forum. 2022;3(8):e-22253-e.
21. Barthold D, Joyce G, Ferido P, Drabo EF, Marcum ZA, Gray SL, Zissimopoulos J. Pharmaceutical treatment for Alzheimer's disease and related dementias: utilization and disparities. J Alzheimers Dis. 2020;76(2):579–89.
22. Lapane KL, Ott BR, Hargraves JL, Cosenza C, Liang S, Alcusky M. Changes in antidementia medications upon admission to the nursing home: who decides and why? Results from a national survey of nursing home administrators. J Am Med Dir Assoc. 2024;25(1):41-6.e5.
23. Ott BR, Hollins C, Tjia J, Baek J, Chen Q, Lapane KL, Alcusky M. Antidementia medication use in nursing home residents. J Ger Psychiatry Neurol. 2024;37(3):194–205.
24. Blanco-Silvente L, Capellà D, Garre-Olmo J, Vilalta-Franch J, Castells X. Predictors of discontinuation, efficacy, and safety of memantine treatment for Alzheimer's disease: meta-analysis and meta-regression of 18 randomized clinical trials involving 5004 patients. BMC Geriatr. 2018;18(1):168.
25. Chin E, Jaqua E, Safaeipour M, Ladue T. Conventional versus new treatment: comparing the effects of acetylcholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonist with aducanumab. Cureus. 2022;14(11): e31065.
26. Ruangritchankul S, Chantharit P, Srisuma S, Gray LC. Adverse drug reactions of acetylcholinesterase inhibitors in older people living with dementia: a comprehensive literature review. Ther Clin Risk Manag. 2021;17:927–49.
27. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical practice guideline for prescribing opioids for pain—United States, 2022. MMWR Recomm Rep. 2022;71(3):1–95.
28. Atee M, Morris T, Macfarlane S, Cunningham C. Pain in dementia: prevalence and association with neuropsychiatric behaviors. J Pain Symptom Manag. 2021;61(6):1215–26.
29. Jourdan J-P, Bureau R, Rochais C, Dallemagne P. Drug repositioning: a brief overview. J Pharm Pharmacol. 2020;72(9):1145–51.
30. Taylor DH Jr, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. J Alzheimers Dis. 2009;17(4):807–15.

Authors and Affiliations

Sadaf Arefi Milani[1] · Jordan Westra[1] · Yong-Fang Kuo[2] · Brian Downer[3] · Mukaila A. Raji[4]

✉ Sadaf Arefi Milani
samilani@utmb.edu

[1] Department of Epidemiology, University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0177, USA

[2] Department of Biostatistics & Data Science, University of Texas Medical Branch, Galveston, TX, USA

[3] Department of Population Health & Health Disparities, University of Texas Medical Branch, Galveston, TX, USA

[4] Division of Geriatric Medicine, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA