Opioid Use in Chronic Pain Patients and Its Implications for Dementia and Alzheimer's Disease Onset: A Scoping Review

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ABSTRACT

Objective: The aim of this scoping review was to examine the current literature on the effects of opioid use influencing the onset of Alzheimer's disease (AD), the most common form of dementia, in patients with chronic pain.

Methods: A comprehensive literature search was conducted using MESH and keywords searches across PUBMED, MEDLINE (OVID), and EMBASE databases. Studies were included if they evaluated both chronic pain and opioid use in relation to dementia or AD onset, reported dementia or AD as either primary or secondary outcomes, and employed primary qualitative or quantitative research designs. Exclusion criteria included articles not published in English, those focusing on acute pain without a chronic component, studies addressing general cognitive decline without specific mention of dementia or AD, and studies investigating opioid use without consideration of chronic pain or dementia/AD as an outcome.

Results: A total of six articles met the inclusion criteria. The majority of the findings indicated an association between opioid use and the onset of dementia or AD in chronic pain patients, with a generally dose-dependent relationship, particularly in populations aged over 50. One study did not establish a causal link between opioid use and dementia onset, while another found an association between chronic pain and dementia independent of opioid use.

Conclusion: This review suggests that opioid use may be linked to an increased risk of dementia onset in chronic pain patients, predominantly in older populations, and that this relationship appears to be dose-dependent. However, further investigation is required to establish causality.

RÉSUMÉ

Objectif : L'objectif de cette étude de la portée était d'examiner la littérature actuelle sur les effets de la consommation d'opioïdes sur l'apparition de la maladie d'Alzheimer (MA), la forme la plus courante de démence, chez les patients souffrant de douleurs chroniques.

Méthodes : Une recherche documentaire exhaustive a été menée à l'aide de MESH et de mots-clés dans les bases de données PUBMED, MEDLINE (OVID) et EMBASE. Les études ont été incluses si elles évaluaient à la fois la douleur chronique et l'utilisation d'opioïdes en relation avec la démence ou l'apparition de la MA, si elles rapportaient la démence ou la MA comme résultat primaire ou secondaire, et si elles utilisaient des modèles de recherche qualitatifs ou quantitatifs primaires. Les critères d'exclusion comprenaient les articles non publiés en anglais, ceux portant sur la douleur aiguë sans composante chronique, les études traitant du déclin cognitif général sans mention spécifique de la démence ou de la MA, et les études examinant la consommation d'opioïdes sans tenir compte de la douleur chronique ou de la démence/MA comme résultat.

Résultats : Au total, six articles répondaient aux critères d'inclusion. La majorité des résultats indiquaient une association entre la consommation d'opioïdes et l'apparition de la démence ou de la MA chez les patients souffrant de douleur chronique, avec une relation généralement dose-dépendante, en particulier chez les populations âgées de plus de 50 ans. Une étude n'a pas établi de lien de causalité entre la consommation d'opioïdes et l'apparition de la démence, tandis qu'une autre a mis en évidence une association entre la douleur chronique et la démence indépendamment de la consommation d'opioïdes.

Conclusion : Cette étude suggère que la consommation d'opioïdes pourrait être associée à un risque accru de démence chez les patients souffrant de douleurs chroniques, principalement chez les personnes âgées, et que cette relation semble être dose-dépendante. Cependant, des recherches supplémentaires sont nécessaires pour établir un lien de causalité.

INTRODUCTION

Chronic pain, usually defined as pain persisting for more than three months, is a prevalent condition affecting millions globally, with significant implications on quality of life and healthcare systems.[1] Annually, approximately one in ten adults are diagnosed with chronic pain, and the global burden of this condition is increasing.[2] In recent years, research has begun to explore a potential link between chronic pain and cognitive decline, with some studies reporting a 42% increased risk of dementia, including Alzheimer's disease (AD), among chronic pain patients.[3] Furthermore, an increased number of parts of the body experiencing chronic pain have been associated with a heightened risk of all-cause dementia.[4]

Mechanistic explanations for the observed connection between chronic pain and cognitive decline have centered on pain-in- duced neuroinflammation and dysfunction in brain regions, such as the frontal cortex and the locus coeruleus (LC), potentially leading to neurodegeneration.[3] Chronic pain has also been shown to activate neuroinflammatory pathways in the brain through prolonged release of pro-inflammatory cytokines (such as IL-1β, TNF-α, and IL-6), and exacerbate cortisol release from the hypothalamic-pituitary-adrenal (HPA) axis, ultimately impairing the hippocampus.[5,6] These neurodegenerative processes overlap with those observed in Alzheimer's disease (AD), where abnormal amyloid beta and tau deposition causes neuroinflammation, dysfunction in neurogenesis, and hippocampal degeneration, ultimately leading to memory loss.[7] One study found individuals with chronic pain maintained a 42% higher risk of dementia, including Alzheimer's disease (AD). Furthermore, an increased number of chronic pain sites has been associated with a heightened risk of all-cause dementia.[4] However, the evidence remains mixed, as some studies have failed to establish a relationship between chronic pain and the long-term risk of dementia as seen by Rouch et al. (2022), while Tian et al. (2023) and Wang et al. (2024) were able to find significant risk increase for AD in chronic pain patients.[3,4,8] The inconsistency between studies may stem from differences in study design, population characteristics, follow-up duration, and methods used to assess pain and outcomes. Beyond the possibility that chronic pain itself may contribute to cognitive decline, there is growing consideration that a class of medications used to manage pain—opioids—might also be playing a role. Opioids are a class of drugs favoured by physicians in the management of chronic pain as this class of drugs provides strong pain relief, is well studied and the dosage for patients is well established. This makes them the preferred treatment for pain, as the pain relief is instantaneous when compared to alternative forms of treatment like physical therapy, and because the side effects and legal status of opioids are more established across many countries in comparison to drugs like cannabinoids.[9,10] When used as directed by a physician, prescription opioids provide relief from pain and exert their analgesic effects by acting on μ-opioid receptors in the nervous system.[11] Beyond the perspective of pain relief, many physicians favour the prescription of opioids to patients with chronic pain as they produce a mild sedation and a sense of well-being or euphoria that aids in the reduction of anxiety and promotes good sleep. Some physicians even believe that it is unreasonable to leave a patient to suffer from chronic pain and that withholding the prescription of opioids is similar to withholding treatment.[10,12]

While opioids are effective in alleviating pain, the long-term cognitive effects of opioid use remain controversial. Some studies suggest a potential link between opioid use and an increased risk of dementia, particularly in older populations. This corresponds to the clinical understanding that dementia primarily affects individuals aged 65 and older, however risk of dementia also increases with age.[13] For example, research indicates that individuals aged 75 to 80 who use opioids may have a 1.39-fold higher risk of developing dementia.[14] However, the literature remains inconclusive, as findings are mixed—while some studies suggest a potential link between opioid use and the onset of AD or other dementias, others have failed to establish a significant association, making it unclear whether a true effect exists.[15] This inconsistency highlights the need for a deeper understanding of the relationship between chronic pain, opioid use, and cognitive decline. It remains unclear whether the observed cognitive effects are primarily driven by chronic pain itself, opioid use, or the interaction between the two. Given the high prevalence of chronic pain, the widespread use of opioids, and the growing aging population, addressing these knowledge gaps is critical to improving patient care and developing preventative strategies against dementia and AD. The objective of this scoping review is to analyze the existing literature examining the relationship between chronic pain, opioid use, and the risk of dementia, including AD. By evaluating studies that consider these factors in combination, this review aims to elucidate which plays a more prominent role in contributing

to cognitive decline. The findings will help inform future approaches to pain management and dementia prevention, ultimately supporting better outcomes for patients at risk of both chronic pain and cognitive impairment.

METHODS

Relevant studies were identified through a systematic search of the electronic databases PUBMED, MEDLINE (OVID), and EMBASE. These databases were selected due to their extensive coverage of biomedical literature and their recognized role in retrieving relevant studies in systematic reviews. Embase and MEDLINE together have been shown to achieve high recall in systematic reviews, retrieving approximately 92.8% of included references, making them foundational for biomedical literature searches.[16] Additionally, previous research has indicated that incorporating databases beyond MEDLINE/PubMed does not significantly alter the included studies or final outcomes of a review.[17] Given the scope of this review, these databases were deemed the most appropriate to ensure comprehensive literature coverage while maintaining methodological feasibility. The search strategy employed a combination of Medical Subject Headings (MESH), title, and abstract terms. Search terms included: ((((“Analgesics, Opioid”[Mesh]) OR “Opiate Alkaloids”[Mesh]) OR (((Opioid*[Title/Abstract]) OR (opiate*[Title/ Abstract])) OR (Pain reliever*[Title/Abstract]))) AND ((“Chronic Pain”[Mesh]) OR (((Chronic pain*[Title/Abstract]) OR (long-term pain[Title/ Abstract])) OR (Non-acute pain[Title/Abstract])))) AND (((“Dementia”[Mesh]) OR “Alzheimer Disease”[Mesh]) OR ((Dementia[Title/Abstract]) OR (Alzheimer*[Title/Abstract])))) Studies were selected based on predefined inclusion and exclusion criteria. The inclusion criteria were: (1) studies examining both chronic pain and opioid use with respect to dementia or AD onset, (2) studies reporting dementia or AD as primary or secondary outcomes, (3) primary studies using qualitative or quantitative designs. The exclusion criteria were: (1) studies not in English, (2) studies focusing solely on acute pain without a chronic component, (3) studies addressing general cognitive decline without specific mention of dementia or AD, and (4) those focusing on opioid use without including chronic pain or failing to mention dementia as an outcome.

After the initial search yielding 753 results (PubMed: 76, MED- LINE: 72, Embase: 605), duplicates were removed, leaving a total of 624 articles. Two independent reviewers screened titles, resulting in 77 articles. An abstract screen reduced this number to 22 articles. After the full-text review, 6 articles remained eligible, with consideration of inclusion and exclusion criteria as shown in **Figure 1**. Discrepancies between reviewers were resolved through consensus. Data extraction focused on study design, population characteristics, opioid types, dosage, chronic pain categorization, and dementia/AD-related outcomes. The studies were evaluated using a scoping review methodology based on the Arksey and O’Malley framework, including five stages: (1) identifying research questions, (2) identifying relevant studies, (3) study selection, (4) data extraction, and (5) summarizing and reporting the results.[18]

RESULTS

This review included six primary studies. The main objective of the studies was to determine the association and relationship between opioids on the incidence of dementia and AD in chronic pain patients. Researchers primarily compared dementia onset in chronic pain patients using opioids with those using non-opioid analgesics or no pain relief at all.[19-24] Some studies also sought to explore dose and duration-dependent effects of opioid use and chronic pain[20,21,24], while others examined age-specific subpopulations to determine if younger or older individuals were more vulnerable to the effects of opioid use on dementia.[23,24] The six primary studies are summarized in **Table 1, Table 2** and **Table 3**, where the dose, duration of treatment with opioids, as well as the impacts of specific age populations and their vulnerability to dementia while using opioids are assessed in greater detail.

These studies, conducted between 2001 and 2022, mainly used data from large cohorts and national health insurance databases. The average age of participants across studies was 68.8 years, with a higher proportion of about 60% female participants compared to males. For the population studied, chronic pain was present at baseline. Various types of chronic pain were considered, including arthropathy/spondylopathy, back and neck pain, pain localized to specific regions such as the facial area, hip, knee, shoulder, and stomach. Additionally, conditions such as osteoarthritis, rheumatoid arthritis were also considered. Neuropathic pain and its variants were also mentioned. The main opioids considered amongst the studies were morphine, fentanyl, oxycodone, buprenorphine, opium, tramadol, methadone, codeine, hydromorphone, dihydroco- deine

and meperidine.[19-24]

In terms of findings, four studies showed a positive association between opioid use in chronic pain patients and increased dementia risk. For instance, the study of Gao et al. (2024) reported that opioid use significantly elevated the risk of dementia in a dose-dependent manner, with higher numbers of opioid prescriptions (over 20) correlating with greater risk.[20] Another study by Bornier et al. (2023) found that chronic pain patients using opioids had a higher incidence of Alzheimer's Disease-Related Dementia (ADRD), and this risk increased with longer durations of opioid use (between 3 and 15 defined daily dose and more than 16 DDDs).[21] Defined daily dose (DDDs) is the cumulative dose over the study period divided by the product's average recommended daily dose to calculate total exposure. In another population of patients with chronic non-cancer pain analyzed by Oh et al. (2024), opioid use was associated with a significantly higher risk of dementia, but this effect was particularly pronounced in individuals aged 60 years and older.[23] Additionally, one study by Sun et al. (2023) showed that the onset of dementia occurred earlier in opioid users

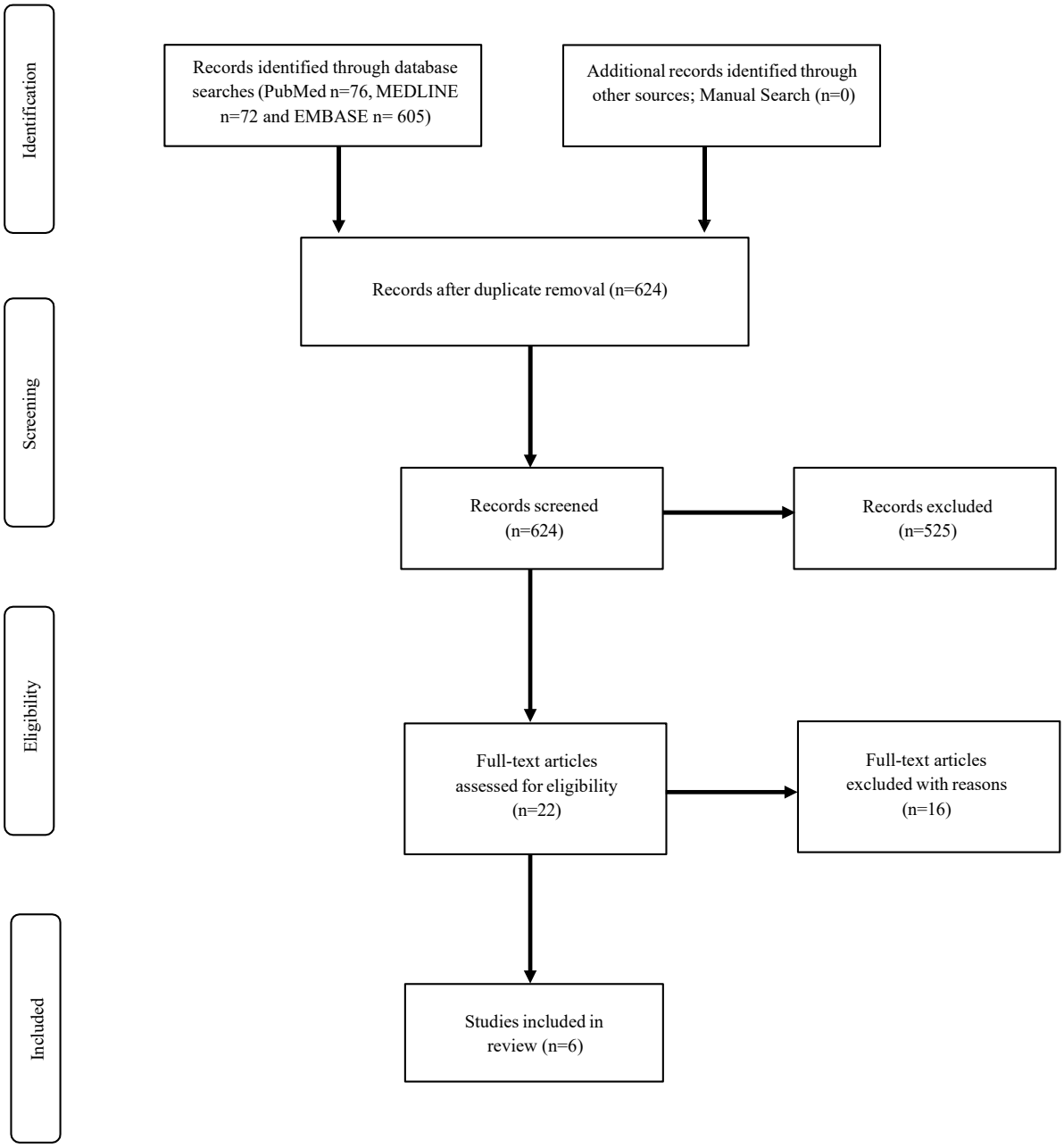

Figure 1. PRISMA Flowchart

Table 1. Summary of findings

Authors	Population	Objectives	Methods	Limitations	Strengths
1. Khalid et al	Older US Medicare beneficiaries with CNCP at baseline, opioids as covariates	Assess the association between CNCP and ADRD risk	Retrospective cohort	Self-report diagnosis of AD and dementia Opioid use used as covariate, not primary independent variable	Examine multisite pain number of sites Controlled for a wide range of potential confounders
2. Gao et al	Patients with CP at baseline, using opioids	Assess the association between regular opioid use with incident dementia and neuroimaging outcomes among CP patients	prospective cohort Case-control (opioid prescriptions) cross-sectional (neuroimaging outcomes)	Observational nature may introduce confounders	Neuroimaging provides visual markers of dementia progression
3. Bornier et al	Pt with CP at baseline, using opioids	Assess the impact of all types of CP and the long-term use of pain medications on the incidence of ADRD	Retrospective cohort	Follow-up bias	Focus on opioid use over time and dose-dependent effects
4. Guo et al	European ancestry GWAS studies on dementia and related conditions. European ancestry GWAS summary statistics on pain-related medication from Wu et al. Summary statistics of CP from Open GWAS and Neale laboratory	Assess the causal relationship between CP, use of analgesics and cognitive status	Bidirectional Mendelian randomization (MR) analysis	MR assumptions (e.g., no pleiotropy) may introduce bias	Only study examining genetic and causal relationships
5. Oh et al	South Korean patients with CNCP as baseline using opioids	Assess the association between opioid use and the development of dementia in CNCP patients	Population- based cohort	Possible distribution bias (only 1.7% of CNCP patients used opioids) CNCP limited musculoskeletal disorders	Large sample size (1,261,682) Analyzed multiple types of dementia (VD, UD and AD)
6. Sun et al	Asian patients with CP at baseline, using opioids	Assess long-term opioid use and dementia risk in patients with CP	Head-to-head propensity score-matched comparative cohort Time-varying cox regression analysis	All Asian population not representative of the general population	Age-stratified analysis Included AD and VD

with chronic pain compared to non-opioid users, with the increased risk appearing after shorter durations of opioid use in those aged 40 years and older compared to younger populations.[24]

Not all findings were consistent, however. The study by Guo et al. (2023), used Mendelian genetic analysis, a type of analysis that investigates the causal correlation between genetic variants and risk factors to a particular disease outcome. This approach was used as it assists in removing genetic biases that can affect observational studies and can establish a better cause and effect relationship between variables. Guo et al. (2023) found no significant causal relationship between opioid use and dementia, though it did report that multisite chronic pain was linked to worsened general cognitive function.[22] This cognitive decline, however, was not specific to dementia or its subtypes. Another study by Khalid et al. (2020) found that chronic pain alone, independent of opioid use, was associated with an increased risk of ADRD.[19]

Moreover, sex-related differences in the association between opioid use, chronic pain, and dementia risk varied across the included studies. Some studies found no significant interaction between sex and dementia risk associated with opioid use (Sun, Gao), while others reported a modestly higher risk in men than women (Oh).[20,24] Specifically, Oh found that opioid use was associated with a 13% higher risk of total dementia in men and a 10% higher risk in women with a similar pattern observed for AD but no significant association with vascular dementia in either sex.[23] Bornier and colleagues found that women with chronic pain had an incidence rate of 12.5 per 1,000 person-years compared to 9.2 in men, a pattern also seen in the control group, suggesting an overall higher baseline risk of ADRD in women.[21] Similarly, Khalid reported that women had a significantly higher incidence of ADRD (6.2%) than men (5.0%) ($P < 0.0001$).[19]

DISCUSSION

Our scoping review explored the relationship between chronic pain, opioid use, and dementia onset across six studies, identifying key themes and some contradictions. A clear theme across all studies is that chronic pain increases the risk of dementia, and this association often increases with the number of pain sites. Regarding opioids, four out of six studies found a significant link between opioid use and increased dementia risk in chronic pain patients[20,21,24,25], with three of these showing a dose-dependent relationship, with higher doses and number of prescriptions linked to greater risk.[20,21,25] One of these studies interestingly saw

Table 2. Study demographics

Study	Time of Data Collection	# Participants (case/control)	Age of cases (SD)	# Sex (case, F/M)
1.	2001–2013	6369/10565	74 (0.07)	4215/2154
2.	2006-2010	17820/53460	58.74 (7.76)	10876/6944
3.	2006-2010	13596/40788	65.6 (10.7)	8386/5210
4.	NA	Multisite chronic pain analysis: 387,649/NA Cognitive function analysis: 22,593/NA dementia analysis: 9,251/248,813 The Alzheimer's disease dataset: 21,982/41,944	NA	NA
5.	2010-2015, Study ended with dementia onset (evaluated from 2016-2022)	21800/1239882	63.8 (11.6)	13534/8266
6.	2004- 2020	20986/20986	81.78 (14.69)	10815/10176

Table 3. Opioid and chronic pain effects on dementia/AD

Study	Opioid Type	Dose-dependent effect of opioid use	CP operationalization	Types of chronic pain	Effects on Dementia
1	NA	NA	Medicare fee-for-service claims	Headache, osteoarthritis, joint, back/neck, and neuropathic pain	Opioid use not significantly associated with ADRD risk NCPC at baseline increased risk for ADRD, with risk rising with more pain conditions
2	NA	Higher prescription number (>20 vs 1-5) associated with dementia risk	Pain for >3 months	Headache, facial, neck/shoulder, back, stomach, hip, knee and general pain	15-year cumulative incidence of opioid use associated with a small but significant increase in dementia risk, particularly with prolonged use.
3	Morphine, oxycodone, tramadol, codeine, fentanyl, others	Duration-dependent, Moderate (>=3 and <= 15 DDDs) and strong (>16 DDDs) opioid Exposure significantly Associated with ADRD frequency	At least 6-months of analgesics use or medical diagnoses of chronic pain according to the International Classification of Disease or by the LTI for chronic pain	Neuropathic, joint/rheumatic & arthropathy/spondylopathy, back, migraine/headache	Chronic pain increased ADRD risk
4	NA	NA	Chronic/Site-specific chronic pain >3 months	Neck, shoulder, headache, hip, stomach/abdominal, back, knee, facial, general and multisite pain	No associations between analgesics use and cognitive function or dementia MCP associated with worse cognitive function, but not dementia. No association of SSCP of general CP with dementia or cognitive decline
5	Fentanyl, morphine, oxycodone, hydromorphone, methadone, codeine, dihydrocodeine and tramadl	NA	CNCP patients (musculoskeletal disorders)	Rheumatoid arthritis, osteoarthritis, low back pain and neck pain	Opioid use associated with 15% higher dementia risk, 15% AD risk and 16% unspecified dementia risk. Only in ≥60 age group
6	Morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, tramadol, codeine, and meperidine.	Higher cumulative opioid use (cDDD) increased risk of dementia	NA	NA	Dementia risk increased significantly for opioid users aged 40+ after 7 years of use, while those aged 30–39 faced risk after 9 years, and those under 30 after 10 years of use

*≥3 and < = 15 DDDs and > 15 DDDs had p values of less than 0.05 and were statistically significant for increased risk of ADRD development according to the Bornier et al. paper. > 15 DDDs was more statistically significant than 23 and < = 15 DDDs for developing ADRD

that compared with persons regularly taking non-opioid analgesics, those taking opioids exhibited lower total grey matter and hippocampal volumes, and higher white matter hyperintensities volumes.[20] Loss of hippocampal volumes has been established as a pathogenesis factor of AD and dementia in previous works.[26,27]

One study that found no association between opioid use and dementia onset only considered opioid use as a covariate without assessing dose nor duration, possibly explaining the discrepancy.[19] Additionally, a Mendelian randomization study found no causal relationship between chronic pain or analgesics and dementia but noted that a higher number of pain sites was linked to general cognitive decline.[22] These findings could stem from the methodology used, suggesting that long-term mechanistic studies, such as those in controlled laboratory settings, may better elucidate causal pathways between chronic pain, opioids, and dementia.

Previous research has primarily focused on the effects of either opioids or chronic pain on cognitive decline and dementia separately. Several studies have specifically linked opioid use to an increased risk of dementia. For instance, a study in Australia demonstrated that chronic opioid use in patients aged 65-69 was associated with worse cognitive function in the Mini Mental State Examination.[28] This test consists of 11 questions designed to test 5 areas of cognitive function: calculation, registration, recall, attention and orientation. Similarly, a national cohort study in Israel found that individuals aged 75-80 who were exposed to opioids had an increased risk of dementia onset and those with heavy opioid use were found to have an increased risk of all-cause dementia.[14,29]

The physiologic mechanisms for opioids potentially being involved in the onset of dementia exist as it is known that the opioid system plays a crucial role in modulating sensory, emotional, cognitive functions, and addictive behaviors. Dysregulation can affect neurotransmitters (acetylcholine, norepinephrine, GABA, glutamate, serotonin) linked to AD. Opioid receptor dysfunction may also lead to increased amyloid-beta (Aβ) production, tau hyperphosphorylation, neuroinflammation, degeneration of cholinergic neurons, and cognitive impairment—all hallmark characteristics of AD.[30] Additionally, alterations in opioid receptor signaling have been linked to elevated levels of BACE1 and γ-secretase enzymes, further contributing to abnormal amyloid-beta accumulation and disease progression.[29,30]

Opioid use may also contribute to dementia by causing structural changes in the brain's white matter, particularly in the corpus callosum, which connects the brain's hemispheres and supports cognitive communication. Prolonged opioid use further disrupts these pathways, potentially accelerating neurodegenerative processes characteristic of dementia. In opioid-dependent individuals, decreased integrity in pathways linked to the amygdala reduces connectivity in key regions, like the anterior insula and nucleus accumbens, affecting emotional regulation and memory.[31] However, not all studies support a definitive link between opioid use and dementia. Some research has suggested that carefully titrated doses of opioids may not cause extensive memory impairment and, in certain cases, may even improve memory.[32] Another study found no significant association between opioid use and increased risk of AD, even with prolonged use or high cumulative doses.[15] Thus, while opioids may play a role in dementia pathogenesis for certain populations, other factors like dosage, duration of use, and individual variability need further investigation to draw conclusive connections.

Emerging research also highlights chronic pain as a significant, yet often overlooked, risk factor for dementia, including AD.[33] Studies suggest that pain experienced in multiple sites may substantially increase the likelihood of developing dementia. For instance, individuals with chronic pain in several locations were found to have a higher risk of both all-cause dementia and AD, emphasizing the need to address pain as part of dementia prevention strategies.[4,34,35] Interestingly, it has been found that it's not the severity of pain, but rather how much the pain disrupts daily life—known as pain interference—that has the strongest link to dementia risk.[36]

To our understanding, our review is one of the first to focus on the existing literature analyzing the risk of dementia onset associated with opioid use specifically in chronic pain patients. This approach allowed us to attempt to isolate the impact of opioids on dementia risk, reducing the effect of chronic pain itself acting as a confounding factor.

The studies in our review exhibit strong methodological rigor by controlling for confounding variables like age, gender, and comorbid conditions, enhancing the robustness of their findings. Large sample sizes, some over a million

participants, provide high statistical power and enhance generalizability. Advanced methodologies, such as neuroimaging and genetic testing, add depth by offering direct insights into structural and functional brain changes and revealing causal relationships. These varied approaches provide complementary evidence, bolstering the credibility of the conclusions on the complex relationship between opioid use, chronic pain, and dementia risk.

The reviewed studies demonstrate several key strengths, of- fering valuable insights into the relationship between chronic pain, opioid use, and the risk of dementia. Oh et al. (2024) and Sun et al. (2023) leveraged large datasets, with Oh et al.'s study drawing from the South Korean NHIS database, which included over 1.2 million patients, giving the study significant statistical power.[23,24] Similarly, Sun et al. (2023) employed advanced statistical techniques, including propensity score matching and time-varying Cox regression analyses, which provided stronger control for confounding variables and improved the accuracy of the association between long-term opioid use and dementia risk.[24] Gao et al. (2024) incorporated neuroimaging data to analyze dementia progression in chronic pain patients, providing visual evidence of the cognitive changes associated with opioid use.[20] This objective marker allowed for a more direct assessment of the biological changes in the brain related to opioid use and chronic pain. The use of a variety of chronic pain types across the studies, from musculoskeletal pain to neuropathic pain, further strengthens the research by accounting for different pain profiles, as shown in Bornier et al.'s study, which considered the long-term effects of opioids across multiple pain conditions.[21] The inclusion of age-stratified analyses in studies like Sun et al. (2023) and Oh et al. (2024) is another major strength.[23] This approach helped identify specific age-related vulnerabilities, showing that older patients were more suscepti- ble to early dementia onset with opioid use. Additionally, Guo et al. (2023) utilized Mendelian randomization, a genetic approach that helped explore causal relationships between opioid use, chronic pain, and cognitive function.

While this method's assumptions can be difficult to verify, it provides an innovative way of disentangling the genetic and environmental contributions to the observed associations, thus expanding the scope of analysis beyond traditional observational designs.[22] Despite the strengths, several limitations temper the findings of these studies. A significant limitation across most of the studies is their reliance on observational designs, which hinders the ability to establish definitive conclusions. For instance, Bornier et al. (2023) and Khalid et al. (2020) relied on data derived from self-reported or claims-based sources.[19,21] This introduces potential bias and misclassification, particularly in diagnosing dementia and tracking opioid use, where inaccuracies in reporting could distort the observed relationships. Moreover, the operational definitions of chronic pain and opioid use varied across studies. Some, like Oh et al. (2024), focused exclusively on musculoskeletal disorders, potentially limiting the applicability of their findings to patients with other forms of chronic pain.[23] This variability in the scope of chronic pain definitions makes direct comparisons between studies more challenging and reduces the generalizability of the results to broader chronic pain populations. Another limitation is the geographic and demographic scope of several studies. Sun et al. (2023), for example, focused solely on Asian populations, and Borner et al. (2023) focused on the French population, which may limit the external validity of the findings to more diverse populations.[24] Differences in healthcare systems, opioid prescribing practices, and population genetics could also affect the outcomes observed, making it difficult to apply these findings universally. In studies such as Guo et al. (2023), the use of Mendelian randomization introduces its own set of limitations. While powerful for causal inference, the assumptions of this method—such as no pleiotropy—are difficult to confirm and could lead to biased estimates of causal relationships.[22] Dementia studies often define "older populations" as those aged 65 and older, but this study included individuals aged 40 and up, introducing variability. This broad range fails to distinguish between early-onset dementia and age-related cognitive decline. Clear age group definitions are crucial for understanding the link between chronic pain, opioid use, and dementia risk.

Despite the methodological strengths across the included studies, several limitations affect the interpretability and generalizability of their findings. Many relied on self-reported data for opioid use and pain severity, which can introduce recall bias and limit the accuracy of exposure assessment. Furthermore, while specific opioids and chronic pain conditions were often considered in isolation, few studies directly compared their relative impacts on dementia risk. This gap hinders our ability to discern whether certain opioids or pain subtypes are more neurotoxic. The inherent difficulty in objectively measuring chronic pain adds another layer of complexity—higher opioid dosages may simply reflect

more severe or widespread pain rather than a causal link to cognitive decline. Inconsistencies in how chronic pain was defined and categorized across studies further complicate cross-study comparisons. Some studies restricted their definitions to musculoskeletal pain, while others included neuropathic or mixed pain conditions, reducing coherence across the literature. These methodological differences emphasize the need for standardized definitions and more objective pain assessments in future research.

Our review was limited to reviewing associations, and not causation. Future research could focus on studying this relationship more closely, potentially using in vivo models or mechanistic studies to establish causality. Another avenue of exploration could involve analyzing objective measures for assessing chronic pain, such as neuroimaging techniques, quantitative sensory testing or inflammatory markers that may correlate with pain levels. These methods could provide a more accurate understanding of pain levels beyond self-reported measures. Moreover, the inconsistent results on sex-related differences should further be studied. Potential explanations worth exploring could be differences in opioid prescribing patterns, pain perception, hormonal influences, social determinants of health and healthcare utilization between men and women. Future research should also explore how sociodemographic factors influence opioid use and dementia risk. Investigating these could improve personalized pain management strategies.

CONCLUSION

This review demonstrates that opioid use in chronic pain patients is generally associated with an increased risk of dementia, with the relationship appearing to be dose-dependent and particularly pronounced in older populations. The findings are significant because they suggest that both chronic pain and opioid use contribute to cognitive decline, emphasizing the need to address both factors in dementia prevention strategies, especially for vulnerable older adults. However, the literature remains inconsistent, with some studies failing to establish a clear link between opioid use and dementia, likely due to differences in study designs, populations, and pain definitions. These limitations highlight the need for more research to establish causality, explore the mechanisms underlying these relationships, and develop objective and consistent methods for assessing chronic pain. Future studies should also investigate the differential effects of various opioid types and pain conditions on dementia risk to inform more targeted and effective pain management practices.

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Conflicts of Interest Disclosure

There are no conflicts of interest to declare.