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Use of analgesics (opioids and nonsteroidal anti-inflammatory drugs) and dementia related neuropathology in a community-based autopsy cohort

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Abstract

BACKGROUND—Opioids may influence the development of Alzheimer’s Disease (AD). Some studies have observed AD pathology in the brains of opioid abusers. No study has examined the association between prescription opioid use and dementia-related neuropathologic changes.

OBJECTIVE—To examine the relationship between prescription opioid or NSAID use and dementia-related neuropathologic changes.

METHODS—Within a community-based autopsy cohort (N=420), we ascertained opioid and nonsteroidal anti-inflammatory drug (NSAID) use over a 10 year period from automated pharmacy data and calculated total standardized daily doses (TSDDs). A neuropathologist assessed outcomes including neuritic plaques, neurofibrillary tangles, and macroscopic infarcts.

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Outcome measures were dichotomized using established cutpoints. We used modified Poisson regression to calculate adjusted relative risks (RR) and 95% confidence intervals (CI), accounting for participant characteristics and using weighting to account for possible selection bias related to selection into the autopsy sample.

RESULTS—Heavier opioid exposure was not associated with greater neuropathologic changes. For neuritic plaques, the adjusted RR [95% CI] was 0.99 [0.64–1.47] for 91+ TSDDs of opioids vs. little to no use, and for neurofibrillary tangles, 0.97 [0.49–1.78]. People with heavy NSAID use had higher risk of neuritic plaques (RR 1.39 [1.01–1.89]) than those with little to no use, as we have previously reported. Neither opioid nor NSAID use was associated with higher risk of macroscopic infarcts or with Lewy body disease.

CONCLUSION—Prescription opioid use is not associated with dementia-related neuropathologic changes, but heavy NSAID use may be. More research is needed examining chronic pain, its pharmacologic treatments and neuropathologic changes.

Keywords

neuropathology; Alzheimer's disease; opioid analgesics; non-steroidal anti-inflammatory agents; neuritic plaques; neurofibrillary tangles

1. Background

In 2010, about 12% of U.S. adults (27.5 million people) received an opioid prescription.[1] Many people use opioids long-term for chronic pain, yet substantial gaps remain in our knowledge about opioids' long-term safety, including effects on the brain.[2] Studies have observed neuropathologic changes in people who have abused opioids resembling the changes seen with Alzheimer's disease (AD).[3, 4] It is not known whether such changes might also occur with use of prescription opioids, including at typical exposure levels.

Basic science studies provide intriguing evidence about the potential impact of opioids on neurons and the brain, but it remains difficult to draw definitive conclusions. While some studies attribute protective effects to opioids, other studies suggest potential harm. For instance, one study reported that morphine exposure protected against neurotoxicity from intracellular A β both in vitro and in vivo and that morphine improved performance on memory tasks in rats with amyloid-related cognitive impairment.[5] On the other hand, morphine decreased neuronal cell density and increased apoptosis in a hippocampal cell culture model,[6] and in mouse fetal brain cells, short-term morphine exposure reduced cell proliferation and increased apoptosis.[6, 7] Morphine also promotes hyperphosphorylation of tau, a key component of neurofibrillary tangles.[8] Taken together, these findings suggest a need to investigate the potential association between prescription opioid use and neuropathologic changes.

One challenge is that chronic pain itself may affect the brain, causing changes such as decreased gray matter volume and density.[9–13] Prior studies could not determine whether these changes were due to chronic pain or to pharmacologic treatments such as opioids. Similarly, in studying medication safety, it can be challenging to separate the effects of a medication from those of the condition it is being used to treat. One common approach is to

compare medications used for the same condition that act through different pathways. If an association is seen for only one of the medication classes, this pattern suggests a causal association rather than confounding. Thus in studies of opioids, it can be helpful to also examine nonsteroidal anti-inflammatory drugs (NSAIDs), which treat pain through a different mechanism.

We previously found that people with the heaviest use of either opioids or NSAIDs had higher dementia risk than people with little to no use. [14] The fact that associations were present for both medication classes could suggest confounding. We also found that heavy NSAID use was associated with higher prevalence of neuritic plaques, one of the hallmark findings of AD. [15] Two prior studies[16, 17] examined the association of NSAID use with AD neuropathology and reported no association, but both studies had limitations including small sample size, which may have led to low power, and lack of information about NSAID dose, duration, or intensity of exposure. No study has examined whether prescription opioid use is associated with neuropathologic changes. Thus, in this study we sought to examine associations between prescription opioid use and neuropathologic changes within a community-based autopsy cohort. To address possible confounding by chronic pain, we also examined NSAID exposure. Compared to our previous study of NSAIDs,[15] the current analyses include 163 more autopsy cases and use an exposure definition harmonized with that used for opioids.

2. Methods

2.1 Overview

This study draws on data from an autopsy series arising from a prospective cohort study of older adults, the Adult Changes in Thought (ACT) study, which is set within Kaiser Permanente Washington, an integrated healthcare delivery system in the Northwest U.S. This healthcare system was previously known as Group Health. In 2017 it was acquired by Kaiser Permanente and so throughout this paper we will refer to this healthcare system as Kaiser Permanente. Study procedures have been previously described[18] and are summarized below. Our primary analyses include ACT participants who died and underwent autopsy. Because these people may differ from participants who were not autopsied, we used statistical methods to account for selection bias.[19] These analyses draw on data from the full ACT study cohort, so both populations are described below. Study procedures are approved by our Human Subjects Review Committee, and participants provide written informed consent.

2.2 Study Population

ACT recruits Kaiser Permanente members living in or near Seattle, Washington who are at least 65 years old, community dwelling, and non-demented. The study enrolled an initial cohort of 2581 from 1994–1996 and another 811 participants from 2000–2003, then in 2004 began ongoing recruitment to maintain a cohort of 2,000 people undergoing follow-up. Study visits every 2 years include an interview, cognitive screening, and physical measurements.

The current study included participants with one or more follow-up visits and at least 10 years of continuous health plan enrollment (defined in relation to an “index date” discussed below). From this base population, we identified all participants who underwent brain autopsy. The ACT study conducts medical record reviews which provide valuable covariate data, so we excluded the 5 autopsied participants lacking these data, leaving 420 autopsies for analyses (Figure 1).

2.3 Defining an Index Date

We needed to specify the time window in which opioid and NSAID exposure would be measured. Our aim was to measure only medication exposure that occurred prior to dementia onset, for several reasons. First, the time period before dementia onset is the most etiologically relevant. Although neuropathologic changes can only be observed after death, it is generally accepted that the neuropathologic changes of AD precede detection of clinical dementia.[20] Also, the presence of dementia might influence subsequent medication exposure, either through use of certain medications to treat dementia symptoms or avoidance of contraindicated medications. Thus, including medication exposures after dementia onset could bias results. For these reasons, it would be problematic to simply specify a set time period prior to death as the exposure window. Instead, we measured medication exposure in relation to an “index date” for each participant. For those who developed dementia, the index date was defined as the estimated date of dementia onset. To define comparable index dates for participants without dementia, we matched each one to a pool of similar participants who had developed dementia (matched on age and year of death or year of ACT enrollment) and randomly selected an index date from the pool (see Supplementary Table 1 for details.) We then measured exposures and covariates in a time window prior to the index date. This approach ensured that for participants who developed dementia, we only included in our analyses the medication exposures which occurred prior to the onset of dementia, as best we could ascertain it. Thus, in our study it is unlikely that the medication exposures described here could have been influenced by (e.g. a consequence of) a participants’ dementia status.

2.4 Medication Exposure

We identified exposure to prescription opioids and non-aspirin NSAIDs using automated pharmacy dispensing data. These data, referred to as prescription fills, capture information about medication purchases at pharmacies within and outside of Kaiser Permanente and indicate that participants actually received the medications of interest. We converted prescription fills to standardized daily doses (SDDs) as in prior studies.[21] To compute SDDs, we multiplied the number of pills that were supplied by the pill strength and a conversion factor.[14, 21] In this analysis, 1 SDD of opioids is equivalent to 30 mg morphine and 1 SDD of NSAIDs to 1200 mg ibuprofen. We then defined each participant’s cumulative opioid and NSAID exposures as the total standardized daily doses (TSDDs), that is, the sum of SDDs across all prescriptions dispensed in the exposure window.

We measured exposure in a 10 year time window from 11 years prior to the index date to 1 year prior to the index date. We selected 10 years because it struck a reasonable balance between having a lengthy enough period to assess long-term cumulative medication exposure (which we hypothesized would be the most harmful) while not excluding too much

of our sample due to requiring that all participants be enrolled in the health care system throughout the exposure window. It also aligned well with our prior research on clinical outcomes.[14] We excluded medication use during the 1 year prior to the index date because prodromal symptoms of dementia could affect medication usage.

We categorized cumulative opioid use as 0–10, 11–90, or 91+ TSDD for all analyses, with cutpoints chosen based on our prior work.[14] To put this in clinical terms, an individual could reach the highest level of exposure by using the equivalent of 30 mg of morphine daily for more than 3 months. For NSAID exposure, the categories were 0–60, 61–540, and 541+ TSDD. We chose different cutpoints for NSAIDs than for opioids because in our population, participants had much higher cumulative exposure to NSAIDs. An individual could reach the highest NSAID exposure category by using the equivalent of 1200 mg of ibuprofen daily for about 1.5 years. For both medication classes we refer to the use categories as “little to no use”, “moderate use”, and “heavy use”.

2.5 Neuropathologic Outcomes

We examined neuropathologic changes associated with dementia, including changes of AD (neuritic plaques assessed by Consortium to Establish a Registry for Alzheimer’s Disease [CERAD] staging criteria,[22, 23] neurofibrillary tangles assessed by Braak staging,[24, 25] and amyloid angiopathy[26]), cerebrovascular disease (cerebral microinfarcts, macroscopic infarcts, and atherosclerosis), Lewy bodies, and hippocampal sclerosis.[20, 27] Evaluations were performed by a board-certified neuropathologist who was blinded to participants’ medication exposure status using methods that have been previously described.[28] Approximately 40% of brains had a post mortem interval of 8 hours or less. The majority of the remainder of brains had post mortem intervals less than 48 hours. Following extraction, brains were fixed in 10% neutral buffered formalin for 10 to 14 days. Density of neuritic plaques was assessed by CERAD criteria on silver stained sections of middle frontal gyrus and inferior parietal lobule using the Bielschowsky staining method.[23] Braak staging for neurofibrillary tangles was assessed using tau-2 immunohistochemistry on sections of middle frontal gyrus, hippocampus at the level of the uncus and occipital cortex including primary visual cortex.[25] Lewy bodies were assessed using anti-alpha-synuclein antibodies (clone LB509) using standard criteria.[29] Gross vascular lesions were counted in formalin-fixed slabs. Microvascular ischemic lesions were assessed in hematoxylin and eosin stained sections of middle frontal gyrus, superior and middle temporal gyrus, inferior parietal lobule, occipital lobe, striatum at the level of the anterior commissure and thalamus according previous methods.[30] Hippocampal sclerosis was assessed on hematoxylin and eosin stained sections of hippocampus at the level of the uncus and lateral geniculate body and was assessed as present if there was complete loss of neurons in the CA1 region. Cerebral amyloid angiopathy was assessed by the presence of Congo red in arteries and arterioles on Congo red stained sections of the occipital lobe.

We dichotomized each outcome measure using cutpoints that have been shown to be associated with clinical dementia[26, 28] and that we have used in our prior work.[15, 26, 28, 31] For neuritic plaques, we compared moderate or frequent versus sparse or none; for neurofibrillary tangles, Braak stages V–VI versus 0–IV; for amyloid angiopathy, any versus

none; for atherosclerosis, moderate or severe versus none or mild; for cerebral microinfarcts, 3 versus 2; and for macroscopic infarcts, 1 versus none. Lewy bodies and hippocampal sclerosis were categorized as present or absent.

2.6 Covariates

ACT study data provided information about age, sex, self-reported race, education, *APOE* genotype, self-rated health, self-reported physical activity, body mass index (BMI), depressive symptoms (using a modified version of the Center for Epidemiologic Studies Depression scale),[32] smoking history, and comorbid illnesses. *APOE* genotyping was performed using standard techniques[33, 34] and dichotomized as any vs. no copies of the $\epsilon 4$ allele. For physical activity, participants were asked how many days per week they did each of the following activities for at least 15 minutes: hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise. Medical records were manually reviewed to collect information about medical conditions including diabetes, stroke, and coronary artery disease (CAD, including myocardial infarction, history of coronary artery bypass grafting, coronary angioplasty, or angina). We identified incident cancer diagnoses through linkage to data from the Western Washington Surveillance, Epidemiology and End Results cancer registry. We defined cancer as present if a participant received a new cancer diagnosis during the 10-year exposure window or the two years prior to this window. Hypertension was defined as receiving 2 or more fills for an antihypertensive medication in a 1-year period, based on computerized pharmacy data which capture medication purchases at pharmacies within or outside of Kaiser Permanente. For analyses, we dichotomized physical activity using a cutpoint of 3 sessions per week, based on our prior work showing that people exercising at or above this level had significantly lower dementia risk than people exercising less than 3 times per week.[35]

For selection models, variables including stroke and CAD were defined from a combination of ACT interview data and electronic health data. This was necessary because selection models include all ACT participants and medical record reviews are not complete for those without autopsy.

For variables that can change over time, we used values from the 10-year exposure window. Comorbid illnesses were defined as present if they were present any time during the window. For self-rated health, depression and physical activity, we used the value closest to the index date, and for BMI, the average over the time window.

Information about participants' dementia status was used in constructing the index date and in the selection model. Methods for diagnosing dementia in ACT have been previously described.[18] Briefly, participants undergo cognitive screening at baseline and at follow up visits every 2 years using the Cognitive Abilities Screening Instrument.[36] People scoring 86 or lower receive a detailed evaluation, including a neuropsychological test battery and examination by a study physician. All available medical records are reviewed, including imaging results. All results are reviewed by a multidisciplinary consensus committee. Dementia diagnoses are assigned using criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.[37] AD diagnoses are made based on the National Institute for Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and

Related Disorders Association (NINCDS-ADRDA) criteria.[38] The date of dementia onset is imputed as the date halfway between the visit triggering the evaluation and the prior study visit.

2.7 Statistical Analysis

We analyzed the associations between cumulative opioid or NSAID exposure and neuropathology outcomes using modified Poisson regression. This approach estimates relative risks by modeling binary outcomes using a Poisson error distribution with log link estimated with generalized estimating equations to account for possible misspecification of the mean-variance relationship.[39] We estimated separate models for each neuropathologic outcome. Primary outcome models adjusted for ACT study cohort (wave of enrollment), age at death, sex, education, hypertension, diabetes, stroke, and CAD. Models for macroscopic infarcts did not adjust for stroke, because of the high overlap expected between these variables. Since opioid and NSAID exposure were included in the same model, estimates for each medication class are adjusted for use of the other class. In sensitivity analyses, we further adjusted for self-rated health, depression, physical activity and BMI. We conducted several post hoc sensitivity analyses: 1) adjusting for APOE $\epsilon 4$ allele status (using complete-case methods); 2) categorizing microscopic infarcts as any vs. none (as opposed to > 2 versus ≤ 2 in primary analyses); 3) adjusting for the presence of cancer; and 4) excluding patients with cancer.

Hippocampal sclerosis and Lewy body disease in the frontal or temporal cortex were relatively uncommon, found in 9% and 6% of the autopsy cohort, respectively. For these outcomes, numbers were too small to support our planned approach to multivariable statistical modeling and so we calculated the prevalence of each outcome according to level of opioid or NSAID exposure.

We conducted additional exploratory analyses of neuritic plaques and neurofibrillary tangles using the full range of values for these measures (i.e., ordinal levels rather than dichotomized values). For these analyses we used ordinal logistic regression instead of the modified Poisson approach, and thus, measures of association estimated from these models are adjusted odds ratios (OR). An OR from these models estimates the relative odds that a person with a given level of opioid exposure would have more severe neuropathologic changes compared to a person with the referent level of opioid exposure, that is, little to no use.

In all statistical modeling, we used inverse probability weighting (IPW) to account for possible selection bias, including the bias that could arise if some characteristics including exposure to opioids or NSAIDs were associated with risk of death (i.e., survivor bias) or with likelihood of consenting to autopsy.[19] We estimated selection weights using a logistic regression model for the probability of selection from the broader ACT cohort into the autopsy study sample. That model included age, ACT study cohort, sex, education, dementia, opioid and NSAID exposure, and history of stroke and CAD. The inverse of the estimated probabilities were used as weights in the main outcome models.

To incorporate uncertainty in the estimated selection weights, we computed bias-corrected and accelerated bootstrap standard errors and 95% confidence intervals for all adjusted relative risk (RR) parameter estimates,[40] as in prior publications.[15, 31] Comparing a 95% confidence level to a null finding of $RR = 1$ or $OR = 1$ corresponds to hypothesis testing using a two-sided significance level of $\alpha = 0.05$.

Analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC) and R, version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

As of September 30, 2012, ACT had enrolled 4,724 people of whom 1874 (40%) had died and 478 had undergone brain autopsy, with 420 eligible for these analyses (Figure 1). Supplementary Table 2 describes characteristics of people who came to autopsy compared to those who did not. Compared to participants who did not undergo autopsy, those who did undergo autopsy were older and had higher prevalence of some comorbid illnesses, as expected. The two groups were very similar in their level of exposure to opioids and NSAIDs.

Table 1 shows characteristics of the 420 participants included in these analyses, including stratified by level of opioid exposure. 184 participants (44%) had little to no opioid exposure during the 10-year exposure window, 177 (42%) had moderate exposure, and 59 (14%) heavy exposure. Among those with heavy exposure, the median TSDD was 196 (interquartile range 131 to 500), which translates to about 6 months of daily use at the standardized daily dose. Compared to people with little to no opioid exposure, a higher proportion of people with heavy exposure were female and had hypertension, diabetes, CAD, or a history of stroke (Table 1). They were more likely to report fair or poor health, to have depression, to have moderate or heavy NSAID exposure, and not to exercise regularly.

Neuropathologic outcomes did not differ significantly according to level of opioid exposure (Table 2). People with heavy opioid exposure and those with little to no exposure were about equally likely to have intermediate or frequent neuritic plaques (53% vs. 48%; adjusted RR 0.99 [95% CI, 0.64–1.47]) and Braak stage V or VI neurofibrillary tangles (32% vs. 29%; adjusted RR 0.97 [0.49–1.78]). No significant differences were seen for other outcomes.

Heavy use of NSAIDs was associated with significantly higher risk of intermediate or frequent neuritic plaques compared to little to no use (adjusted RR 1.39, 95% CI [1.01–1.89]). The risk of Braak stage V or VI for neurofibrillary tangles was higher with heavy NSAID use (RR 1.51, 95% CI [0.87–2.57]), though this finding was not statistically significant. No substantial differences were seen for other outcomes.

In sensitivity analyses that adjusted for self-rated health, depression, physical activity and BMI, results were essentially unchanged. Results did not change materially with adjustment for *APOE* genotype. When we examined microscopic infarcts categorized as any vs. none, there continued to be no association with use of opioids or NSAIDs. For example, the RR for any microscopic infarct was 0.82 (95% CI 0.54–1.19) comparing heavy opioid use to little or no use (for comparison, this RR was 0.84 [95% CI 0.37–1.69] in primary analyses).

For heavy NSAID use, the RR was 1.09 (0.77–1.47) compared to little or no use, while in primary analyses it was 0.67 (95% CI 0.28–1.45). Analyses that either adjusted for the presence of cancer or excluded participants with cancer did not yield substantially different results.

Supplementary Table 3 shows results from sensitivity analyses of neuritic plaques and neurofibrillary tangles that used ordered categories for outcomes rather than dichotomous variables. Heavy opioid use was not associated with greater odds of having more neuritic plaques, nor did there appear to be a dose-response relationship with this outcome across the opioid exposure categories: the OR for moderate opioid exposure (11–90 TSDD) was 1.27, while the OR for heavier use (91+ TSDD) was 1.20. These results do not suggest a pattern of higher risk with increasing exposure to opioids. In contrast, moderate NSAID use (61–540 TSDD) was associated with a moderate increase in neuritic plaques (OR 1.47) compared to little or no NSAID use, while heavy NSAID use (>541 TSDD) was associated with an even greater increase (OR 1.94, 95% CI 1.08–3.47). Neither opioid nor NSAID use was significantly associated with odds of having more neurofibrillary tangles. The ORs for both heavy NSAID and heavy opioid use (compared to little or no use) were elevated to a similar degree (OR approximately 1.5), with wide confidence intervals that included the null, indicating that neither association was statistically significant (Supplementary Table 3).

Table 3 provides descriptive information about hippocampal sclerosis and about Lewy body disease in the frontal or temporal cortex, outcomes for which numbers were too small to support our planned statistical modeling approach.

4. Discussion

In this community-based autopsy cohort, people with heavier use of prescription opioids did not have a higher risk for dementia-associated neuropathologic changes than people with little to no use. In contrast, people with the heaviest use of NSAIDs were more likely to have AD neuropathologic changes than people with little to no use, as we have previously reported.[15]

To our knowledge, this is the first study to examine neuropathologic changes associated with use of prescription opioids. Two prior studies examined neuropathologic changes in young people who had abused opioids.[3, 4] Ramage et al. found that compared to age-matched non-drug users, young people who had abused opioids were more likely to have neurofibrillary tangles and to have β -amyloid precursor protein immunoreactivity in the hippocampus and brainstem.[4] Similarly, Anthony et al. observed higher levels of hyperphosphorylated tau in the brains of 39 people who had abused opioids than in age-matched, cognitively normal controls.[3] In addition, Cao et al. reported that in rat cortical neurons, morphine induced tau hyperphosphorylation,[8] which is relevant because hyperphosphorylated tau is an important component of neurofibrillary tangles. There are several possible explanations for differences between these studies' findings and ours. We studied a very different population, older adults, and a different exposure, prescription opioids. The specific opioids used and the level of exposure are likely very different in our study than in prior studies. If opioids do have harmful effects, the overall level of exposure

in our study may have been below the threshold needed for harmful effects. The people in earlier studies who abused opioids may have had other exposures putting them at risk. Heroin and other street drugs are not pharmaceutical quality and may contain toxic substances. People in prior studies used other illicit drugs that could have contributed to brain pathology. Finally, our much older population would be expected to have a higher baseline prevalence of plaques and tangles, and it may be that in the context of a heavier burden of neuropathologic changes, a contribution from prescription opioids is more difficult to detect.

In this study, people with heavy NSAID use had more neuritic plaques than people with little to no use, a finding that was statistically significant. They also had a higher neurofibrillary tangle stage, although this association was not statistically significant. We previously reported similar findings from analyses in a subset of these data.[15] Our findings contrast with two prior papers that did not observe an association between NSAID use and AD neuropathology.[16, 17] However, the prior studies had limitations which could have obscured an association if one does exist. First, they had relatively small sample sizes. The study by Beeri et al. included only 56 autopsies in people exposed to NSAIDs, compared to 198 in our study. Both prior studies lacked information about dose, duration or intensity of NSAID use and relied predominantly on a dichotomous measure (any vs. no NSAID exposure). In contrast, our heavy use category consisted of people who had filled enough prescriptions to allow them to take a standardized daily dose of NSAIDs every day for 1.5 years. Arvanitakis et al.[16] noted that their participants appeared to use NSAIDs sporadically and so they might have failed to detect effects of regular, long-term use. Beeri et al.[17] collected information from medical records for the time period in which participants were enrolled in their study, which was on average 3 years prior to death. This time window is unlikely to be the etiologically relevant time period for the development of dementia-related neuropathologic changes. Because most of their participants had already developed dementia, it is likely that AD neuropathologic changes had begun many years previously, long before the exposure window used in their analyses. Thus, methodologic differences could explain the apparent discrepancy between our findings and those of prior studies.

Our findings should be considered in the context of our previous work. In a study of the entire ACT cohort, we observed a modestly higher risk of dementia and AD in people with the heaviest use of either opioids or NSAIDs compared to people with little or no use.[14] For opioids, the adjusted hazard ratio (HR) for dementia was 1.29 (95% CI 1.02–1.62) comparing people with the heaviest use (91+ TSDD) to those with little to no use, and for NSAIDs, the adjusted HR was 1.31 (1.07–1.62) comparing the heaviest users (541+ TSDD) to those with little to no use. These findings motivated the current analysis. It is somewhat unexpected that in the current study we observed AD-associated neuropathologic changes with heavy NSAID use but not heavy opioid use. If confounding by chronic pain explained our prior findings for dementia, we might have expected to observe similar neuropathologic changes with heavy use of either NSAIDs or opioids, since both groups suffer chronic pain. The contrasting findings we observed for neuropathologic changes with NSAIDs vs. opioids may reflect these medications' differing biological effects. Alternatively, these contrasting results might stem from differences in the extent of use of each medication class in our

population. The “heaviest use” group for opioids consisted of people with 91+ TSDDs over a 10-year period (median 196 TSDDs) while for NSAIDs, it included people with 541+ TSDDs (median 1550 TSDDs). Perhaps the association seen for NSAIDs with neuropathologic outcomes reflects the greater extent of exposure to this medication class or to chronic pain, for which NSAID exposure is a proxy. We believe that taken together, the findings from this work and our prior work suggest that the association between NSAID use and dementia may be mediated in part by AD-associated neuropathologic changes.[15] No clear explanation for the modest association between opioid use and dementia is yet apparent.

This study has several strengths. Data come from a large community-based autopsy cohort. Participants in the ACT study are recruited at random from those meeting eligibility criteria within a source population that is representative of the general population in the Pacific Northwest. We have access to computerized pharmacy data about medication exposures going back many years. The ACT study’s rich data allow adjustment for many potential confounders. We used statistical methods to account for potential selection bias. We also created definitions of medication exposure that were specifically designed to assess medication exposure prior to the onset of dementia, making it less likely that medication exposure could be a consequence of dementia or neuropathologic changes.

This study also has limitations. Few participants had very heavy exposure to opioids. Although the number of autopsies was large compared to prior studies, we still had limited power. Confidence intervals were fairly wide. For most analyses, our estimates are sufficiently precise to rule out an effect size on the order of 2 or greater, but an increased risk of smaller magnitude could still be clinically important. For some outcomes such as hippocampal sclerosis, small numbers precluded us from conducting the planned statistical modeling and hypothesis testing.

While we were able to study exposure over many years, we did not have information about more remote exposures, such as opioid exposure in mid-life. NSAIDs are available over the counter, and while our data include over-the-counter medications purchased at health plan pharmacies, participants likely also consumed NSAIDs purchased outside of the system. There may be confounding by unmeasured characteristics including chronic pain. The ACT study did not collect information about pain and so we were unable to adjust for the presence of chronic pain or its severity or duration. As shown in Table 1, people with heavy use of opioids were different from those with little to no use in many ways that we were able to measure. They had more comorbid illnesses, including depression, and were more likely to be obese and less likely to exercise regularly. While we used adjustment and inverse probability weighting to address the differences we could measure, there could still be residual confounding by unmeasured characteristics.

We also did not routinely collect information about the indication for use of NSAIDs or opioids. There could be residual confounding if NSAIDs and opioids are used for different clinical indications which convey differing risk of neuropathologic changes, e.g. if NSAIDs were primarily used for inflammatory conditions. In our clinical setting, most people who use either NSAIDs or opioids do so for musculoskeletal and degenerative conditions such as

chronic back pain and osteoarthritis, making it less likely that confounding due to underlying inflammatory conditions is responsible for our findings. Finally, we did not measure amyloid beta protein deposited as senile plaques. Initially, we chose to focus on neuritic plaques, complex lesions that combine both amyloid and tau components. We prioritized this outcome because it is a widely used and standardized measure of the independent contribution of amyloid pathology when measured in combination with neurofibrillary tangles. In 2012, we began collecting Thal phase data (a consensus method for assessing amyloid plaques)[41] for all new autopsies. As these data accumulate, we will investigate this outcome further.

In conclusion, in this large community-based autopsy study, we did not observe higher risk of dementia-associated neuropathologic changes in people with the heaviest exposure to prescription opioids. Our findings suggest increased risk with the heaviest exposure to NSAIDs, as we have reported previously.[15] The association we previously observed between heavy opioid use and dementia risk[14] may not be causal, since we could not identify neuropathologic findings underlying this association. Alternatively, it may be that opioids act through a different pathway which does not produce the neuropathologic findings we examined, or that current techniques are not well suited to detect the effects of opioids on the brain. Basic science studies suggest that opioid exposure may reduce the number of neuronal cells, decrease neuronal progenitor cell proliferation, and increase apoptosis,[6, 7] which could conceivably lead to cognitive impairment without an increase in neurofibrillary tangles or neuritic plaques. If opioid exposure decreases cognitive reserve, it may enhance the impact of existing neuropathologic changes, ultimately leading to dementia.

Management of chronic pain in older adults remains a challenging clinical problem. All available medications convey important risks. While more information is available about NSAIDs' adverse effects, there are ongoing concerns about opioid safety. Results from this study – the first to examine neuropathologic changes with prescription opioid use – suggest that in older people, exposure to a moderately large amount of prescription opioids is not associated with dementia-related neuropathological changes. Nevertheless, major gaps in the evidence base about opioid safety remain. Further research is needed to clarify the relationship between use of prescription opioids and dementia and to elucidate the mechanisms through which opioids may act on the brain.

Supplementary Material

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Figure 1.
Study sample for neuropathology analyses. Abbreviations: ACT, Adult Changes in Thought.

Table 1

Characteristics of the autopsied sample, overall and by cumulative opioid exposure *

	Opioid exposure			
	Total	Little/none (0–10 TSDD)	Moderate (11–90 TSDD)	Heavy (91+ TSDD)
	N=420	N=184	N=177	N=59
	n (%)	n (%)	n (%)	n (%)
Age at death, yrs, median (IQR)	89 (84, 93)	89 (84, 93)	89 (84, 93)	88 (85, 92)
Female	241 (57.4)	103 (56.0)	98 (55.4)	40 (67.8)
White race	404 (96.2)	178 (96.7)	168 (94.9)	58 (98.3)
Education: At least some college	275 (65.5)	116 (63.0)	119 (67.2)	40 (67.8)
APOE ε4 status [†]	115 (30.0)	55 (32.0)	39 (24.5)	21 (40.4)
Treated hypertension	287 (68.3)	120 (65.2)	123 (69.5)	44 (74.6)
Diabetes ^{††}	64 (15.2)	24 (13.0)	25 (14.1)	15 (25.4)
History of stroke ^{††}	107 (25.5)	37 (20.1)	48 (27.1)	22 (37.3)
Coronary artery disease ^{††}	148 (35.2)	57 (31.0)	65 (36.7)	26 (44.1)
Cancer ^{**}	68 (16.2)	25 (13.6)	33 (18.6)	10 (16.9)
Systemic lupus erythematosus ^{***}	2 (0.5)	0 (0.0)	1 (0.6)	1 (1.7)
Rheumatoid arthritis ^{***}	8 (1.9)	0 (0.0)	6 (3.4)	2 (3.4)
Fair or poor self-rated health	141 (33.7)	46 (25.1)	62 (35.0)	33 (55.9)
Depression [‡]	89 (21.3)	31 (16.8)	36 (20.5)	22 (37.9)
Regular exercise [§]	232 (55.4)	105 (57.4)	101 (57.1)	26 (44.1)
BMI: obese ^{††}	50 (11.9)	18 (9.8)	22 (12.4)	10 (16.9)
TSDDs of NSAIDs [*]				
0–60	222 (52.9)	122 (66.3)	84 (47.5)	16 (27.1)
61–540	135 (32.1)	49 (26.6)	56 (31.6)	30 (50.8)
541+	63 (15.0)	13 (7.1)	37 (20.9)	13 (22.0)
Diagnosed with dementia during study follow-up	185 (44.0)	73 (39.7)	79 (44.6)	33 (55.9)
Yrs before death, median (IQR)	4 (3, 6)	5 (3, 6)	5 (3, 7)	4 (2, 5)

Abbreviations: BMI, body mass index; IQR, interquartile range; TSDD, total standardized daily doses; NSAIDs, nonsteroidal anti-inflammatory drugs.

* Medication exposure defined during a 10 year window prior to the index date. See Methods for more information. Percentages are of non-missing data. Less than 1% of data were missing for self-rated health, depression, and exercise. For *APOE* genotype, data were missing for 9% of participants overall, including 7% of those with little to no opioid use, 10% of those with moderate use, and 12% of those with heavy use. No data were missing for other variables.

[†] Presence of one or more *APOE* ε4 alleles.

^{††} From medical records.

^{**} New cancer diagnosis during the 10-year window in which opioid exposure was identified, or the 2 prior years, ascertained through linkage to the Western Washington Surveillance, Epidemiology and End Results cancer registry.

*** Defined from International Classification of Diseases, version 9 diagnosis codes in electronic health data. These conditions were considered to be present if 2 or more diagnosis codes were recorded during the 10 year window in which medication exposure was measured.

[†]Score of 10 on modified Center for Epidemiologic Studies Depression questionnaire.[32]

[§]Exercising for 15 or more minutes at least 3 times per week.

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Table 2

Association between opioid or NSAID exposure and neuropathologic changes

Cumulative opioid exposure*				Cumulative NSAID exposure*		
	Little to no use (0–10 TSDD) N=184	Moderate use (11–90 TSDD) N=177	Heavy use (91+ TSDD) N=59	Little to no use (0–60 TSDD) N=222	Moderate use (61–540 TSDD) N=135	Heavy use (541+ TSDD) N=63
	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]
Alzheimer's disease-associated changes						
Neuritic plaques ^{††}						
None/sparse	95 (52)	83 (47)	28 (47)	119 (54)	64 (47)	23 (37)
Intermediate/frequent	89 (48)	94 (53)	31 (53)	103 (46)	71 (53)	40 (63)
RR (95% CI) ^{**}	Ref.	1.19 (0.92–1.58)	0.99 (0.64–1.47)	Ref.	1.30 (0.99–1.74)	1.39 (1.01–1.89)
Neurofibrillary tangles						
Braak stage 0–IV	130 (71)	120 (68)	40 (68)	161 (73)	90 (67)	39 (62)
Braak stage V–VI	54 (29)	57 (32)	19 (32)	61 (27)	45 (33)	24 (38)
RR (95% CI) ^{**}	Ref.	1.13 (0.75–1.70)	0.97 (0.49–1.78)	Ref.	1.51 (0.97–2.36)	1.51 (0.87–2.57)
Amyloid angiopathy						
None	129 (70)	123 (70)	37 (63)	152 (69)	100 (75)	37 (59)
Any	54 (30)	52 (30)	22 (37)	68 (31)	34 (25)	26 (41)
RR (95% CI) ^{**}	Ref.	0.98 (0.66–1.46)	1.38 (0.78–2.49)	Ref.	0.70 (0.44–1.07)	1.28 (0.79–1.97)
Cerebrovascular disease						
Cerebral microinfarcts						
0–2	154 (84)	153 (87)	46 (79)	188 (86)	111 (82)	54 (86)
3 or more	29 (16)	23 (13)	12 (21)	31 (14)	24 (18)	9 (14)
RR (95% CI) ^{**}	Ref.	0.74 (0.38–1.40)	0.84 (0.37–1.69)	Ref.	1.18 (0.67–2.09)	0.67 (0.28–1.45)
Macroscopic infarcts ^{***}						
0	113 (63)	108 (62)	43 (73)	133 (61)	91 (69)	40 (65)
1	65 (37)	66 (38)	16 (27)	84 (39)	41 (31)	22 (35)
RR (95% CI) ^{**}	Ref.	0.97 (0.68–1.37)	0.60 (0.31–1.05)	Ref.	1.01 (0.67–1.53)	0.97 (0.58–1.52)

	Cumulative opioid exposure*				Cumulative NSAID exposure*			
	Little to no use (0–10 TSDD) N=184	Moderate use (11–90 TSDD) N=177	Heavy use (91+ TSDD) N=59	Little to no use (0–60 TSDD) N=222	Moderate use (61–540 TSDD) N=135	Heavy use (541+ TSDD) N=63		
	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]
Atherosclerosis								
None/mild	75 (42)	64 (38)	23 (41)	86 (40)	52 (41)	24 (39)		
Moderate/severe	104 (58)	106 (62)	33 (59)	131 (60)	74 (59)	38 (61)		
RR (95% CI) **	Ref.	1.08 (0.86–1.35)	0.86 (0.58–1.21)	Ref.	1.21 (0.95–1.52)	1.04 (0.75–1.38)		
Lewy body disease								
Substantia nigra or locus ceruleus								
None	155 (84)	154 (88)	51 (86)	191 (86)	117 (87)	52 (83)		
Any	29 (16)	22 (13)	8 (14)	30 (14)	18 (13)	11 (17)		
RR (95% CI) **	Ref.	0.69 (0.33–1.41)	0.62 (0.20–1.68)	Ref.	1.09 (0.49–2.32)	1.83 (0.70–4.60)		
Amygdala								
None	145 (83)	142 (86)	49 (91)	181 (85)	107 (86)	48 (81)		
Any	30 (17)	24 (14)	5 (9)	31 (15)	17 (14)	11 (19)		
RR (95% CI) **	Ref.	0.88 (0.45–1.73)	0.47 (0.13–1.67)	Ref.	1.03 (0.48–2.12)	1.59 (0.65–3.50)		

Abbreviations: ACT, Adult Changes in Thought; CAD, coronary artery disease; NSAID, nonsteroidal anti-inflammatory drugs; RR, relative risk; TSDD, total standardized daily doses. *Over a 10 year window prior to index date.

[†] n's may not sum to total N in each category due to missing values for some outcomes. Percentages are of nonmissing values. No cases were missing data for neuritic plaques or neurofibrillary tangles. For other outcomes, the number and percent of cases missing were as follows: amyloid angiopathy, 3 cases (0.7%); cerebral microinfarcts, 3 (0.7%); macroscopic infarcts, 9 (2.1%); atherosclerosis, 15 (3.6%); Lewy body disease in the substantia nigra or locus ceruleus, 1 (0.2%); Lewy body disease in the amygdala, 25 (6.0%).

^{††} Consortium to Establish a Registry for Alzheimer's Disease scoring system.

^{**} Adjusted and weighted relative risk. Primary models adjusted for ACT study cohort (wave of enrollment), age at death, sex, education, hypertension, diabetes, stroke, and CAD. Models for macroscopic infarcts did not adjust for stroke because of the high overlap expected between these variables. Since opioid and NSAID exposure were included in the same model, estimates for each medication class are adjusted for use of the other class.

^{***} Cystic infarcts and acute or subacute infarcts.

Table 3

Prevalence of hippocampal sclerosis or Lewy bodies in the frontal or temporal cortex, according to opioid or NSAID exposure status

	Cumulative opioid exposure*			Cumulative NSAID exposure*		
	Little to no use (0–10 TSDD) N=184	Moderate use (11–90 TSDD) N=177	Heavy use (91+ TSDD) N=59	Little to no use (0–60 TSDD) N=222	Moderate use (61–540 TSDD) N=135	Heavy use (541+ TSDD) N=63
	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]	n (%) [†]
Hippocampal sclerosis	19 (11)	15 (9)	1 (2)	19 (9)	8 (6)	8 (14)
Lewy bodies						
Frontal or temporal cortex	16 (9)	7 (4)	1 (2)	13 (6)	8 (6)	3 (5)

Abbreviations: TSDD, Total Standardized Daily Doses.

* Over a 10 year window prior to index date, excluding the year immediately before the index date (because use might have been influenced by prodromal symptoms of dementia).

[†] Percentages shown are of nonmissing data. Data were missing for less than 1% of autopsies regarding Lewy bodies in the frontal or temporal cortex. For hippocampal sclerosis, data were missing for 4% of the group overall, including 4% of those with little to no opioid use, 5% with moderate use, and 3% with heavy use, as well as 5% with little to no NSAID use, 3% with moderate NSAID use, and 6% with heavy NSAID use.