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Original Research Article

Pain in Patients with Different Dementia Subtypes, Mild Cognitive Impairment, and Subjective Cognitive Impairment

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Abstract

Objective. To assess the pain prevalence, pain intensity, and pain medication use in older patients with a diagnosed subtype of dementia, mild cognitive impairment (MCI), or subjective cognitive impairment (SCI).

Design. Cross-sectional.

Setting. Outpatient memory clinics.

Subjects. In total, 759 patients with Alzheimer's disease (AD), vascular dementia, mixed AD and vascular pathology (MD), frontotemporal dementia, dementia with Lewy Bodies, MCI, or SCI.

Methods. Self-reported presence and intensity of pain, prescribed medication, and related descriptive variables were given for each group. To compare groups on prevalence of pain, logistic regression analyses were adjusted for age, gender, and mood. Differences in pain intensity were tested using a Kruskall-Wallis test, and differences in analgesic use with chi-square analyses.

Results. Pain prevalence ranged from 34% in MD to 50% in SCI. AD (odds ratio [OR] = 0.56, 95% confidence interval [CI] = 0.34–0.93) and MD (OR = 0.45, CI = 0.20–0.98) patients were less likely to report pain than SCI patients. The self-reported pain intensity did not differ between groups. In total, 62.5% of patients did not use any analgesic medication despite being in pain, which did not differ significantly between groups.

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Conclusion. Outpatient memory clinic patients with mild to moderate AD and MD are less likely to report pain than patients with SCI. No difference in self-reported pain intensity was present. The high percentage of patients with and without dementia who do not use analgesics when in pain raises the question of whether pain treatment is adequate in older patients.

Key Words. Pain; Dementia; Alzheimer's Disease; Pain Treatment

Introduction

The worldwide aging of the population is invariably associated with an increase in the prevalence of aging-associated conditions, including chronic painful conditions [1]. As a consequence, a significant increase in the number of older adults suffering from chronic pain can be anticipated. The prevalence of painful conditions in older individuals has been estimated to be as high as 50% [2]. The impact of this increase in pain prevalence may be substantial as pain has been associated with numerous comorbid problems including an increased risk of falls [3], neuropsychiatric symptoms (e.g., anxiety and depression) [4], and a lower quality of life [5]. Aging is also an important risk factor for the development of dementia [6]. Studies have demonstrated that in older individuals with dementia, the prevalence of chronic painful conditions may be comparable with that of individuals without dementia [7].

Until recently, research has focused on pain in individuals with dementia without specifying the subtype of dementia or included only individuals with Alzheimer's disease (AD) [8]. However, it has been suggested that the experience of pain may differ between dementia subtypes [8]. Studies focusing on patients with AD have revealed mixed results, showing diminished [9–11], unaltered [12], or even potentially increased pain experience [13,14] compared with healthy controls. Pain experience may be reduced in frontotemporal dementia (FTD) compared with healthy controls [15]. Studies on the association between pain and vascular dementia (VaD) and mixed AD and vascular pathology, referred to as mixed dementia (MD), suggest that individuals with VaD and MD experience the pain more intensely or have more pain locations than older individuals with AD and controls [16–18]. No studies have focused on the experience of pain in dementia with Lewy Bodies (DLB). However, considering the typical neuropathology of DLB, one would expect that the pain experience is similar to that of older individuals with AD [19].

The aim of our study was to provide the first overview of pain prevalence in older individuals suffering from different dementia subtypes, namely AD, VaD, MD, FTD, DLB, and mild cognitive impairment (MCI), as well as subjective cognitive impairment (SCI). First, we will assess the prevalence of pain, pain intensity, and the use of analgesic medication. Second, we will assess whether pain prevalence differs between clinical groups (i.e., dementia subtypes and MCI) and a control group of elderly individuals with subjective memory complaints adjusted for demographic variables and mood. It is hypothesized that pain prevalence is lower in older adults with AD than in older adults with VaD, MD, MCI, or SCI. No difference in pain prevalence is expected between AD, FTD, and DLB.

Methods

Study Design

This cross-sectional study included patients recruited from three outpatient memory clinics in Amsterdam, Amstelveen, and Zutphen, the Netherlands. All patients were referred to a memory clinic with cognitive complaints. Patients were included in this study if they were older than age 60 years and excluded if they were primarily mentally disabled (e.g., Down syndrome), had a primary psychiatric disorder based on clinical diagnosis, had insufficient command of the Dutch language, or if they indicated verbally and/or nonverbally that they did not wish to participate despite earlier consent. Data collected conform with the declaration of Helsinki. The data collection took place prospectively between 2014 and 2015 in Amsterdam and Amstelveen. In Zutphen, existing clinical data, which were collected between 2004 and 2015, were used for all eligible patients.

The cohort of Amsterdam/Amstelveen consisted of 212 patients with a diagnosis of AD, MD, VaD, FTD, DLB, MCI, or SCI. Subsequently, patients were excluded for not completing the pain assessment (N = 15). The baseline sample of Zutphen consisted of 660 patients with a diagnosis of interest. Subsequently, patients (N = 93) were excluded for missing pain data, leaving 567 patients available for analyses. In order to reliably interpret the self-reported presence and intensity of pain, patients with an Mini-Mental State Examination (MMSE) score lower than 12, indicating severe cognitive impairment, were excluded as well (N = 5) [20].

The clinical diagnosis of dementia was based on consensus within a multidisciplinary team using the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for dementia due to Alzheimer's disease [21], the National Institute of Neurological Disorders and Stroke (NINDS) Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria for vascular dementia [22], the revised criteria for FTD [23], and the revised criteria for DLB [24]. The clinical diagnosis of dementia included computed tomography (CT) or magnetic resonance imaging (MRI) as part of the standard diagnostic process. MCI was diagnosed according to National Institute on Aging and Alzheimer's Association (NIA AA) criteria [25]. Finally, the presence of SCI was established in those patients who visited the

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clinic for subjective complaints and did not show any indication of cognitive impairment or a psychiatric or neurological disorder that could account for their complaints.

Pain Assessment

In Amsterdam and Amstelveen, pain was assessed using the Brief Pain Questionnaire–short form (BPI) [26]. The BPI is used to assess the presence of pain and the pain intensity. The presence of pain was assessed by asking the patients whether they had pain today other than everyday kinds of pain (e.g., minor headaches, sprains, and toothaches). Pain intensity was assessed by asking the patients to rate the intensity of their pain on average and in the last 24 hours. Pain intensity is scored on an 11-point scale, with higher numbers indicating more severe pain.

In Zutphen, pain was assessed in two ways. The first assessment took place during a general physical examination as part of the clinical diagnostic procedure, in which all patients were questioned about their physical complaints, including pain complaints. Pain intensity was assessed using an 11-point numerical rating scale, which was identical to that used in Amsterdam and Amstelveen.

Mood

Mood was assessed using the Geriatric Depression Scale–short form [27]. The GDS is a 15-item self-report questionnaire with a maximum score of 15 points. The GDS has been validated against the ICD-10 and DSM-IV diagnosis of depression in older individuals, both with and without dementia, and has shown acceptable validity and specificity in individuals with an MMSE score of 15 points or higher [28–30].

Education

Education was scored with an adapted version of the Verhage seven-point ordinal rating scale [31]. The original scale is: 1 = less than primary education, 2 = completed primary education, 3 = primary education with incomplete secondary education, 4 = complete secondary education, 5 = four years of secondary education, 6 = pre-university education and/or higher vocational education, and 7 = academic degree. In the adapted version, the first four points have been taken together to represent lower education, while the other points remain unchanged.

Medication Use

Medication use was assessed by using a list of the prescribed medication provided by the pharmacy or primary physician. For the current study, only medication that conformed to the Anatomical Therapeutic Chemical classification system—N02 analgesics, N03 anticonvulsants, N05 psycholeptics, N06A antidepressants, and M01A nonsteroidal anti-inflammatory drugs (NSAIDs)—were included. The NSAID medication was added to the analgesics to create a single analgesic medication variable. In addition, an additional analgesic variable was computed that included analgesics and all types of medication that may be used as off-label pain medication (i.e., N02 analgesics, N03 anticonvulsants, N05 psycholeptics, N06A antidepressants, and M01A NSAIDs). The use of the included medications was dichotomized into present or absent.

Chronic Diseases

Information about the presence of chronic diseases was obtained from the primary physician and from the medical status. The chronic diseases were grouped into cardiovascular disease (CVD) and diabetes. The cardiovascular diseases include coronary artery diseases, atrial fibrillation, congestive heart failure, cardiomyopathy, transient ischemic attack, cardiovascular accident, and hypertension. The presence of CVD and diabetes was dichotomized. For the analyses, the presence/absence of diabetes and the presence/absence of CVD were used.

Statistical Analyses

Descriptive data are presented for all dementia groups, MCI, and SCI. The FTD and DLB group were excluded from further analyses due to a limited sample size. Differences in demographic variables, pain intensity, and medication use between the dementia subtypes (AD, MD, and VaD), MCI, and SCI were assessed using chi-square or Kruskall-Wallis tests. In the case of a significant group effect with Kruskall-Wallis tests, post hoc Dunn-Bonferroni tests were computed.

Logistic regression analyses were performed to test the associations between dementia subtype, MCI, and SCI and "presence of pain," adjusted for demographic variables and mood. In the first logistic regression analysis, SCI was used as the reference group, and in the second AD was the reference group. Education level was not correlated with the presence of pain and was therefore not included as possible confounder. Statistical analyses were performed using SPSS 21.0 software. Results were considered statistically significant at a P value of less than 0.05.

Results

Patient Characteristics

In total, 759 patients were included in the present study, with a median age of 79 years (interquartile range [IQR] = 75–84 years). The groups differed on age (Kruskal-Wallis $H(4) = 60.69$, $P < 0.001$). Post hoc analyses indicated that patients with MD were older than patients with AD, VaD, MCI, and SCI and that in addition patients with AD and MCI were older than patients with SCI. Half of the patients were female, which did not differ between groups. As expected, the MMSE score

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Table 1 Demographic characteristics

	AD (N = 282)	MD (N = 53)	VaD (N = 56)	MCI (N = 235)	SCI (N = 95)
Age, y	80.0 [77.0–84.3]	83.0 [80.0–87.0]	78.0 [75.0–82.8]	79.0 [74.0–83.0]	76.0 [70.0–81.0]
Female, No. (%)	175 (62.1)	29 (54.7)	26 (46.4)	129 (54.9)	56 (58.9)
Education level (1–4)	1 [1–2]	2 [1–3]	2 [1–3]	2 [1–3]	2 [1–3]
MMSE (0–30)	23.0 [19.0–25.0]	22.0 [19.0–25.0]	23.0 [21.0–26.0]	27.0 [25.0–28.0]	28.0 [27.0–29.0]
GDS (0–15)	2.0 [1.0–3.0]	3.0 [2.0–5.0]	3.0 [2.0–5.0]	2.0 [1.0–3.0]	2.0 [1.0–4.0]
Comorbidity					
CVD present, No. (%)	163 (57.8)	42 (80.8)	44 (78.6)	156 (66.7)	61 (64.2)
Diabetes present, No. (%)	43 (15.2)	14 (26.9)	8 (14.3)	47 (20.1)	16 (16.8)

Values are presented as median [interquartile range] or as stated.
AD = Alzheimer's disease; CVD = cardiovascular disease; GDS = Geriatric Depression Scale; MCI = mild cognitive impairment; MD = mixed Alzheimer's and vascular pathology; MMSE = Mini-Mental State Examination; SCI = subjective cognitive impairment; VaD = vascular dementia.

Table 2 Pain characteristics

	N	AD (N = 282)	MD (N = 53)	VaD (N = 56)	MCI (N = 235)	SCI (N = 95)
Pain present	759	97 (34.4)	18 (34.0)	25 (44.6)	96 (40.9)	47 (49.5)
Pain and analgesic use	757	120 (42.6)	28 (54.9)	30 (52.6)	122 (52.1)	55 (57.9)
Pain intensity (0–10), median (IQR)*	212	0 [0–3.5]	0 [0–5]	0 [0–5]	1 [0–5.5]	1 [0–5]
Chronic pain (≥90 d)†	175	10 (22.2)	7 (20.0)	2 (22.2)	20 (40.0)	6 (27.3)
Medication use, No. (%)						
Analgesics	750	55 (19.7)	15 (30.0)	20 (35.7)	60 (25.9)	26 (27.4)
Antidepressants	753	11 (3.9)	7 (13.5)	3 (5.4)	12 (5.2)	8 (8.4)
Anticonvulsants	753	7 (2.5)	0	4 (7.1)	5 (2.1)	4 (4.2)
Psycholeptics	753	14 (5.0)	8 (15.4)	1 (1.8)	6 (2.6)	5 (5.3)

Values are presented as No. (%) or as stated.
AD = Alzheimer's disease; MCI = mild cognitive impairment; MD = mixed Alzheimer's and vascular pathology; SCI = subjective cognitive impairment; VaD = vascular dementia.
*Not all patients in Zutphen were asked to rate their pain intensity.
†Pain chronicity has not been assessed in Zutphen.

differed significantly between groups (Kruskal-Wallis $H(4) = 282.46$, $P < 0.001$), and post hoc Dunn-Bonferroni analyses indicated that individuals with MCI and SCI had a significantly higher MMSE performance than each of the dementia groups. The dementia groups did not differ significantly with regard to MMSE score. Overall, the number of depressive symptoms was low (2.0 points, IQR = 1–4), although the GDS score did differ between groups (Kruskal-Wallis $H(4) = 23.61$, $P < 0.001$). Patients with AD and MCI reported fewer depressive symptoms than patients with VaD and MD. Patient characteristics are presented in Table 1 and Supplementary Table S1 for FTD and LBD.

Pain Characteristics

The pain characteristics are presented in Table 2 and Supplementary Table S2 for FTD and LBD. No statistical difference in self-reported pain intensity was observed between the dementia subtypes, MCI, and SCI.

Pharmacological Pain Treatment

Overall, 37.5% of patients with self-reported pain used analgesics. The percentage of analgesic medication use and reporting pain did not differ significantly between groups. See Figure 1 for an overview. When analgesics and all possible types of off-label analgesics were combined, 43.4% of patients with pain received potential pain medication.

In total, 63 (29.7%) patients with an available NRS score reported a pain intensity of 4 or higher (median = 6.00, IQR= 5.00–7.00), indicating moderate to severe pain [32]. Analgesics were used by 55.6% of these patients.

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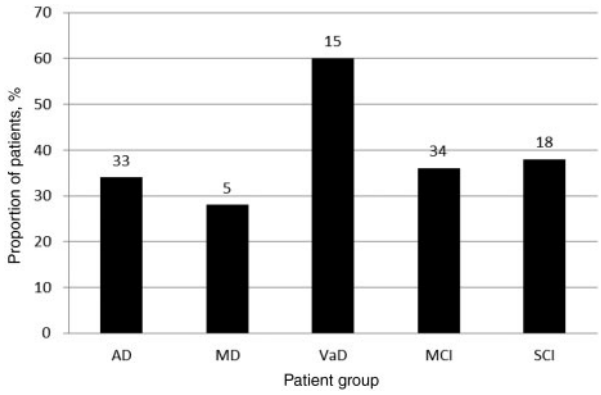

Figure 1 Analgesic use in patients reporting pain. Both absolute numbers and proportion of patients that use analgesics when suffering from pain are presented. AD = Alzheimer's disease; MCI = mild cognitive impairment; MD = mixed Alzheimer's and vascular pathology; SCI = subjective cognitive impairment; VaD = vascular dementia.

This percentage increased to 65.1% when possible off-label analgesics were also included.

Difference in Pain Prevalence Between Dementia Subtypes (i.e., AD, MD, VaD), MCI, and SCI

Table 3 shows that the full model was the best predictive model for pain prevalence (Nagelkerke $R^2 = 0.05$, χ^2 (7, N = 673) = 23.61, $P = 0.001$). Patients with AD and MD have, respectively, chances that are 0.56 and 0.45 times lower of reporting being in pain than patients with SCI.

Difference in Pain Prevalence Between Dementia Subtypes (i.e., MD, VaD), MCI, SCI, and AD

In order to assess whether the presence of pain differed between AD and the other subgroups, AD was used as the reference group. Table 3 shows that the full model was the best predictive model (Nagelkerke $R^2 = 0.05$, χ^2 (7, N = 673) = 23.61, $P = 0.001$). Patients with SCI are 1.79 times more likely to report a painful condition than patients with AD. The presence of pain did not significantly differ between AD and any of the other participant groups.

Discussion

The goal of the present study was to provide an overview of the prevalence and intensity of pain and the use of analgesic medication in patients with a diagnosis of AD, VaD, MD, FTD, DLB, or other age-related cognitive complaint, that is, mild cognitive impairment (MCI) and subjective cognitive impairment (SCI). In addition, differences in the self-reported presence of pain were assessed for each of the dementia subtypes; MCI and SCI were adjusted for demographic variables and mood.

Our results indicate that the self-reported prevalence of pain is lower in patients with AD and MD than in patients with SCI. The observed prevalence of pain for AD (34.4%) and MD (34.0%) is consistent with earlier studies in outpatients with AD (34–35%) [33–35] and MD (31.7%) [34]. However, contrary to our expectations, we did not find a significant difference in the prevalence of pain between AD and VaD. A higher prevalence of pain in VaD was expected based on the (neuro)pathology of this disorder. In VaD, the presence of vascular lesions in the brain that compromise white matter tracts may increase the presence and experience of pain due to deafferentiation [19]. In addition, pain is known to be an important comorbidity in patients with cardiovascular problems [36]. To date, only a limited number of studies have addressed pain in patients with vascular dementia. No pain studies have been performed in outpatients with VaD. In nursing homes, the prevalence of pain does not seem to differ significantly between VaD and other subtypes of dementia [16]. However, patients with VaD and MD do report more painful locations than patients with AD [16], and a higher pain affect in VaD compared with patients without dementia has also been reported [18,37].

Although the relevance of studying pain in older individuals with cognitive impairment has been known for 25 years, the treatment and detection of pain in this patient group are still topics of debate [38].

Analgesic medication use for patients who indicated that they were in pain varied between 27.8% for MD and 60.0% for VaD, but this difference did not reach significance. In total, 29.7% of patients reported moderate to severe pain, of whom 55.6% used analgesics. Earlier research has suggested that there may be suboptimal treatment of pain in elderly people with dementia [8]. In the current study population, the degree of suboptimal treatment appears to be limited. Still, almost one in three patients report clinically relevant pain, of whom only half receive treatment. These numbers cannot be exclusively explained by problems with the assessment of pain in dementia as it even occurs when a person is correctly identified to experience pain [7]. One explanation for the apparent suboptimal treatment of pain is that not all types of pain are treated with analgesics. In 2006, a taskforce of the European Federation of Neurological Societies (EFNS) published a comprehensive review addressing the treatment of neuropathic pain, in which they presented evidence for the successful pain-relieving capabilities of antidepressants, anti-epileptics, and anticonvulsants for different types of neuropathic pain [3]. Still, even after we incorporated all these types of medication and analgesics into one pain medication score, the idea of an apparent suboptimal treatment of pain remains as 34.9% of participants with moderate to severe pain intensity do not receive any of these types of medication. Another possible explanation

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Table 3 Association between presence of pain and clinical groups with SCI or AD as reference (N = 674)

		SCI Reference Group			AD Reference Group		
		OR	95% CI	*P*	OR	95% CI	*P*
Group	AD	0.56	0.34–0.93	0.02	1.00		
	MD	0.45	0.20–0.98	0.05*	0.80	0.40–1.60	0.48
	VaD	0.69	0.34–1.41	0.31	1.24	0.66–2.33	0.51
	MCI	0.70	0.42–1.15	0.16	1.25	0.86–1.81	0.25
	SCI	1.00			1.79	1.08–2.98	0.02
Nagelkerke	R^2	0.05**			0.05**		

Adjusted for age, sex, and mood.
AD = Alzheimer's disease; MCI = mild cognitive impairment; MD = mixed Alzheimer's and vascular pathology; SCI = subjective cognitive impairment; VaD = vascular dementia.
*$P < 0.05$.
**$P < 0.001$.

for the low analgesic use may be the physicians' fear of the negative effects of polypharmacy, pharmacokinetic changes, and pharmacodynamic changes in older patients [39,40]. These fears may be warranted given that, especially for moderate to severe pain, evidence concerning the safety and efficiency of pharmacological treatments in older adults is scarce [41]. This may lead to physicians being more inclined to prescribe nonpharmacological interventions, which were not included in the present study.

Limitations

One of the limitations of our study is that the control group without dementia is not a true control group. The patients in the SCI group were all referred to the outpatient memory clinic for cognitive screening after having reported cognitive complaints. Only patients in whom these cognitive complaints were not the result of underlying psychiatric conditions, primary neurological disorders, or chance findings were included. In addition, all adults were cognitively intact, in that they did not show any evidence of cognitive impairment on extensive neuropsychological testing. Nonetheless, these individuals may not form a truly accurate representation of the normal population. Previous research has also found that patients with SCI are younger than patients with MCI or dementia [42]. The SCI group in the current study has a higher pain prevalence than AD and MD despite being younger. The reasons for the subjective experience of cognitive impairment in SCI are known to be varied, including, among others, sleep disorders, medical disorders, and substance use [42]. These factors are also known to be associated with pain; for example, sleep disturbances are positively associated with pain sensitivity and pain tolerance [43–45] and may explain the higher prevalence of pain in the SCI group. In addition, depressive symptoms may play a role as these symptoms share multiple interactions with pain [46,47]. These symptoms may have influenced our study findings. However, the self-reported intensity of depressive symptoms was relatively low in our sample and was controlled for in the analyses. The validity of the GDS is reduced, much like other self-report questionnaires, in patients with severe cognitive impairment. Nonetheless, given the relatively high median MMSE score in the current sample, it is unlikely that the validity of the GDS is significantly compromised. Finally, patients were not questioned about the potential conditions for which medication was prescribed; although we were unable to determine the reason for prescribing the potential analgesic medication, even after including these types of medication, the notion of an apparent suboptimal pain treatment in older patients persisted.

Due to the small number of patients, the FTD and DLB subgroups were not included in the analyses. Still, it is important to present the data concerning the pain characteristics of these groups. To date, studies concerning pain in these subtypes of dementia have proven scarce, which is likely due to their low prevalence (for FTD) or the difficulty in correctly diagnosing the condition (for DLB and potentially FTD). Presenting these data despite small numbers may enable future researchers to pool the results with other studies in which these subtypes were present in insufficient numbers to be included in the analysis.

Conclusions

The prevalence of self-reported pain in outpatient memory clinic patients with the dementia subtypes AD, VaD, and MD, or MCI or SCI, ranges widely. In a mild to moderate state of dementia, older patients with AD and MD are less likely to report suffering from pain than patients with SCI. The self-reported pain intensity does not appear to differ between the dementia subtypes, MCI, and SCI. Overall, more than half of the patients, both with and without dementia, do not use analgesic medication when in pain. Further research is necessary

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to determine whether pain treatment is adequate in older patients.

Authors' Contributions

All authors were involved in the design of the study, and acquisition of the subjects was performed by TB, EO, and JO. Analyses and interpretation of the data were performed by TB and AM. All authors were involved in the drafting of the manuscript and approved the final version to be published.

Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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