

Review Article

A Review of Pain Prevalence in Alzheimer's, Vascular, Frontotemporal and Lewy Body Dementias

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Key Words

Pain · Alzheimer's disease · Vascular dementia · Frontotemporal dementia · Lewy body dementia

Abstract

Background: Numerous studies have reported on pain in dementia. It has been hypothesized that pain perception differs between dementia subtypes, and therefore, the prevalence of pain differs between dementia subtypes. However, there remains a paucity of evidence on the differences in the prevalence of pain in different dementia subtypes. This review aimed to determine the prevalence of pain for the major dementia subtypes: Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB). **Summary:** We found 10 studies that met our inclusion criteria. Most of these studies reported on AD; studies reporting the prevalence of pain in people with DLB were scarce, and for FTD, we found no studies. The sample-weighted prevalence of pain could only be calculated for AD, VaD and mixed dementia: AD 45.8% (95% confidence interval, CI: 33.4–58.5%), VaD 56.2% (95% CI: 47.7–64.4%) and mixed dementia 53.9% (95% CI: 37.4–70.1%). **Key Messages:** Studies investigating the prevalence of pain in dementia subtypes were scarce; however, we found a high prevalence of pain in dementia without significant differences between the dementia subtypes. More studies are required to draw firm conclusions on the differences in the prevalence of pain between dementia subtypes.

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Introduction

Pain in people with dementia is a common problem, and in view of the demographic changes and aging world population, more people can be expected to suffer from both dementia and a painful condition in the near future [1–4]. The prevalence of pain in people with dementia has been estimated to be approximately 50%, and it has been suggested that the prevalence of pain differs between dementia subtypes [5].

Neuropathological changes differ between dementia subtypes, and these are held responsible for the decline in function as well as for alterations in pain perception [3, 5]. For example, pain perception in Alzheimer's disease (AD) may be altered because of a loss of grey matter, which leads to an increased pain tolerance without a change in pain threshold [6, 7]. Pain experience in vascular dementia (VaD) may increase because of white matter lesions, while pain experience in frontotemporal dementia (FTD) may decrease because atrophy predominates in the frontal cortex [8]. This area is related to emotional states and motivation, which may explain the frequently reported loss of awareness of pain in people with FTD [9]. Pain perception in dementia with Lewy bodies (DLB) may be altered due to brain damage caused by Lewy bodies and cortical atrophy [10]. As our understanding of the underlying neuropathology has increased, it seems worthwhile to take into account the dementia subtype in the management of pain in people with dementia. However, the prevalence of pain has not been determined systematically for each dementia subtype [8, 11].

Our objectives were to determine the prevalence of pain per dementia subtype in published studies that focused specifically on one of the four major dementia subtypes (i.e. AD, VaD, FTD and DLB) in samples from both the community and long-term care facilities (LTCFs) [12]. Because of the differences in neuropathological changes, we hypothesized that the prevalence of pain differs between the four dementia subtypes.

Methods

Search Strategy

We searched MEDLINE, EMBASE, CINAHL and PsycINFO for articles about patients with a known dementia subtype and pain. Databases were searched from inception until August 2014. The search strategy consisted of a combination of free terms and medical subject headings (e.g. MeSH) relating to pain and the 4 commonest subtypes of dementia (i.e. AD, VaD, FTD and DLB). Articles were screened for dementia subtype and pain in the title or abstract text. Additionally, we identified studies by handsearching reference lists of published literature reviews on pain in dementia and studies that met our inclusion criteria. There were no language restrictions.

Selection of Studies

For inclusion, studies had to meet the following criteria: presenting primary data including prevalence of pain in patients with a dementia subtype diagnosis. Studies were independently screened for eligibility on titles and abstract by two reviewers (T.T.B./J.v.K.), and after both reviewers reached consensus, they reviewed the full text of the thus selected papers. Studies that reported pain for both cognitively intact and cognitively impaired patients were included if they reported the results separately to enable data extraction of pain prevalence per dementia subtype. We excluded studies that used pain as an inclusion or exclusion criterion, studies on induced pain (e.g. [13]), case reports or case series. Authors were contacted when studies reported one or more dementia subtypes, but did not display the results of the subtypes separately. Papers were subsequently excluded if the authors were not able to provide the required data or did not respond to our request.

Data Extraction and Synthesis

Two reviewers independently extracted data on study design, setting, population, dementia subtype, prevalence of pain and measurement instruments. For one study, published in Spanish, data was extracted by only one reviewer, who had knowledge of the Spanish language.

We assessed the external and internal validity of the study findings using the Methodological Evaluation of Observational Research (MORE) checklist, which was adapted to the specific research question [14]. External validity is defined as the extent to which the results of a study can be generalized to the target population. For this study, the checklist comprised the following questions:

- Was the sampling frame a close representation of the target population?
- Was an appropriate case definition used for dementia (subtype)?
- Was dementia stage measured in the target population?
- Was some form of random selection used to select the sample?
- Was the likelihood of nonresponse bias minimal?

Internal validity is defined as the possible amount of error in measuring the conditions and was addressed by the following question:

- Was an acceptable pain assessment tool used for the assessment of pain?

For each criterion, three options were possible: '+' = low risk of bias, '-' = possible risk of bias or '?' = risk of bias unclear (due to poor reporting). Each study was rated independently by two reviewers. A total score was calculated as the sum of the individual criteria using a score of '1' for low risk of bias and a score of '0' for possible or unclear risk of bias. Scores for the criterion 'nonreponse' were only reported in two studies; therefore, we decided to exclude this criterion from the total score. We independently extracted information and scores for validity, and all discrepancies were resolved by consensus. We qualitatively evaluated individual studies for similarities and differences in study design and results.

Analysis

The sample-weighted averages with 95% confidence intervals (CI) were calculated for subgroups that consisted of ≥ 100 participants. We used a random-effects model if the I^2 statistic was greater than 50%, and a fixed-effect model if the I^2 statistic was under 50% [15, 16]. Statistical analyses were performed using MedCalc for Windows, version 5.5, 32 bit (MedCalc Software, Ostend, Belgium). In subgroups consisting of < 100 participants, we confined ourselves to descriptive analyses.

Results

The initial electronic search yielded 2,374 hits: 475 from MEDLINE, 1,151 from EMBASE, 311 from CINAHL and 437 from PsycINFO. After removing duplicates, a total of 1,709 articles were screened for eligibility based on title and abstract. Another 4 publications were identified by reference checking and a total of 85 underwent full-text review (fig. 1). We contacted 16 authors for further information and five of them provided additional information. The main reasons for exclusion were no data on prevalence of pain and no data on dementia subtype. Eventually, 10 studies met all inclusion criteria. The characteristics and main findings of the included studies are described in table 1.

All studies were published in the last 10 years. Eight studies were conducted in Europe [17–25] and two studies in the USA [26, 27]. Five studies examined outcomes in nursing homes [23–27], whereas five studies examined outcomes in community-dwelling people or patients recruited from outpatient clinics [17, 18, 20–22]. Five studies were cross-sectional [17, 21, 22, 24, 25, 27], two longitudinal observational studies [19, 23], one was a case-control study [18], one a retrospective cohort study [26] and one a randomized controlled trial [20]. The mean subject age ranged from 70 to 86 years. Three studies focused solely on people with AD [17, 21, 22, 27], five studies included people with AD, VaD, mixed pathologies and/or DLB [20, 23–26], one study was a case-control study of AD and DLB [18] and one study included dementia subtypes based on motor neuron symptoms (i.e. parkinsonian syndromes) [19]. No study reported the prevalence of pain specific to people with FTD.

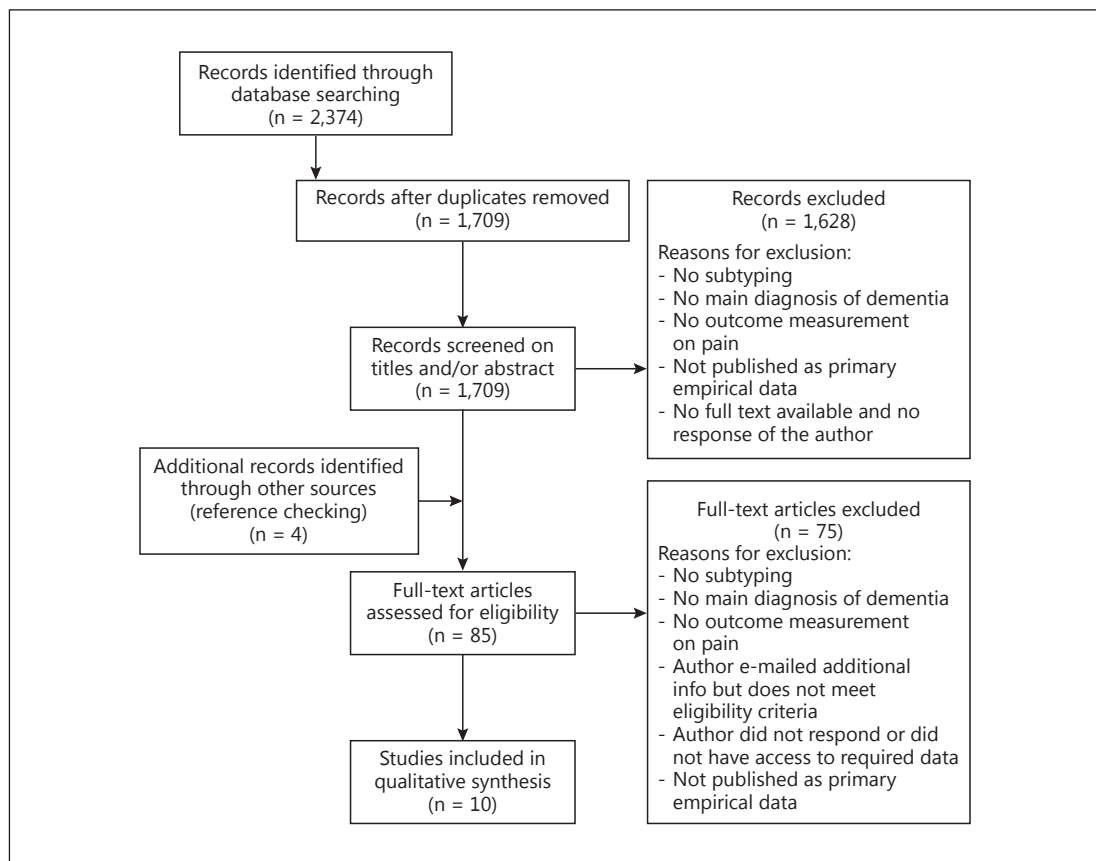


Fig. 1. Study selection process.

Different instruments for pain measurement were reported; four studies used the EQ-5D [17, 18, 20, 21], two studies the Minimum Data Set (MDS) [25, 27], one study the Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale [24], one study the Discomfort Behavioural Scale (DBS) [26], one study a questionnaire that included pain domains [19], and in one study, the physician assessed if pain was present [23].

Risk Assessment

Most studies did not meet all criteria for validity for observational studies. The nonresponse rate was only reported for two studies. With respect to the external validity, the risk of bias was considered possible in most studies, and the most frequent source of bias was found in the random selection of participants. Additionally, with respect to the internal validity, the risk of bias of the measurement of pain was considered low in most of the studies. Only two studies used a nonspecific measurement tool, and in one study, a proxy was asked to fill in or help to fill in the EQ-5D (table 2).

Overall Sample

The 10 published reports provided information on 51,810 participants. Except for one study, which provided information on 49,627 patients, the sample size ranged from 48 to 929. Most studies included more women than men, except for the studies by Colosimo et al. [19] and Boström et al. [18], which both included people with DLB. The mean age of the

Table 1. Studies reporting prevalence of pain in dementia subtypes

First author	Study design	Setting	Dementia subtype(s)	Mean age in years (SD), range	Female	Dementia severity	Mean MMSE score (SD), range	Pain instrument	Pain prevalence
Baquero [17], 2009, Spain	cross-sectional	outpatients with and without AD who donated material to biobank (n = 141)	AD (n = 128)	76.2 (NA), 48–93	68%	GDS 4 27.7% GDS 5 30.5% GDS 6 27.0% GDS 7 5.7%	12.3 (6.89), 0–26 (n = 121)	EQ-5D	no pain 53% moderate pain 41% intense pain 6%
Bostrom [18], 2007, Sweden	case-control	outpatients with AD and DLB (n = 68)	AD (n = 34)	78.2 (NA), 63–92	44%	NA	16.9 (NA), 0–30	EQ-5D	31% (n = 9) intensity: no pain 64.8% mild-moderate 29.4% severe 0% missing 5%
			DLB (n = 34)	77.4 (NA), 64–87	44%		17.3 (NA), 0–17		70% (n = 17) intensity: no pain 20.6% mild-moderate 29.5% severe 20% missing 29.4%
Colosimo [19], 2010, Italy	cross-sectional longitudinal observational study	outpatients with parkinsonism (n = 1,302)	CBD (n = 11)	70.1 (10.2), range NA	56.5%	NA	MMSE <23.5 55% MMSE <23.5 93% MMSE <23.5 24%	questionnaire with five pain domains	36.4%
			DLB (n = 14)	74.1 (6.5), range NA	14.3%				50%
			PSP (n = 30)	69.7 (6.3), range NA	46.7%				40%
Jensen-Dahm [20], 2012, Denmark	baseline data randomized controlled trial	community-dwelling people with AD and other dementia subtypes (n = 321)	AD (n = 239) 74.5% Mix (n = 82) 22.5%	76.2 (7.1), range NA	54.8%	NA	24 (2.6), 20–30	EQ-5D, self-report vs. proxy	33.9% (self-report), 50.2% (proxy) 31.7% (self-report), 42.7% (proxy)
'HR quality of life of Canary Island citizens' Oliva-Moreno [22], 2010 and Lopez-Bastida [21], 2006, Spain	cross-sectional	community-dwelling people with AD (n = 243)	AD (n = 237)	75.5 (8.5), range NA	70.9%	mild 20% moderate 40% severe 40%	NA	EQ-5D	68.6%

Table 1 (continued)

First author	Study design	Setting	Dementia subtype(s)	Mean age in years (SD), range	Female	Dementia severity	Mean MMSE score (SD), range	Pain instrument	Pain prevalence
Buchanan [27], 2005, USA	cross-sectional	residents from LTCFs who live in special care units (SCU) and who do not live in special care units (nSCU) (n = 49,627)	AD (SCU, n = 11,311)	80.6 (7.9)*	62.1%	CPS 2 6.6% CPS 3 44.1% CPS 4 16.3% CPS 5 26.7% CPS 6 5.0%	NA	MDS-pain	no pain 78.8% mild pain (pain less than daily) 14.4% moderate pain 6.2% excruciating pain 0.6%
			AD (nSCU, n = 38,316)	82.5 (8.2)**	69.7%	CPS 2 10.5% CPS 3 37.7% CPS 4 12.7% CPS 5 18.0% CPS 6 15.2%			no pain 71.3% mild pain 17.8% moderate pain 9.5% excruciating pain 1.3%
Hendriks [23], 2015, The Netherlands	longitudinal observational study	baseline characteristics from residents of LTCFs with dementia (n = 372)	AD (n = 147) 46%	84 (7), range NA	70%	advanced dementia 9%	NA	Frequency assessed by physicians	never 47.6% rarely 19.7% sometimes 15.6% often 9.5% almost daily 7.5%
			VaD (n = 72) 23%						never 43% rarely 19.5% sometimes 19.5% often 9.7% almost daily 8.3%
			Mix (n = 65) 18%						never 47.7% rarely 18.5% sometimes 16.9% often 10.8% almost daily 6.1%
			DLB/PD (n = 18) 5%						never 50% rarely 27.8% sometimes 11.2% often 5.5% almost daily 5.5%
Husebo [24], 2008, Norway	cross-sectional	residents from LTCFs with and without dementia (n = 181)	AD (n = 45) 25%	84.7 (6.7), 65–103	75%	CDR 0 17% CDR 1 18% CDR 2 23% CDR 3 43%	12.3 (9.7), 0–30	MOBID-2 Pain Scale	51.1% mean pain score 2.4, SD 2.2, range 0–7
			VaD (n = 66) 37%						56.1% mean pain score 2.5, SD 1.7, range 0–8
			Mix (n = 32) 18%						68.8% mean pain score 2.9, SD 1.9, range 0–7

Table 1 (continued)

First author	Study design	Setting	Dementia subtype(s)	Mean age in years (SD), range	Female	Dementia severity	Mean MMSE score (SD), range	Pain instrument	Pain prevalence
Monroe [26], 2012, USA	retrospective between-groups cross-sectional design at the end of life	residents from LTCFs with dementia (n = 48)	AD (n = 43) 90% VaD (n = 4) 8% DLB (n = 1) 2%	86 (8), range NA	54%	CPS 2 14.6% CPS 3 22.9% CPS 4 20.8% CPS 5 16.7% CPS 6 25.0%	NA	DBS	46.5% mean DBS score 6, SD 8, median 0, range 0–32 50% mean DBS score 15, SD 22, median 6, range 0–48 100% mean DBS score 6
Volker [25], 2009, The Netherlands	cross-sectional	residents from LTCFs with dementia (n = 929)	AD (n = 406) 44.8% VaD/Mix (n = 470) 51.1%	84.5 (7), 65–102	74.5%	CPS 2 7.4% CPS 3 34.6% CPS 4 7.1% CPS 5 36.2% CPS 6 12.2%	NA	MDS-pain Frequency Intensity	50.2% Intensity: no pain 52.4% mild 22.7% moderate 21.4% severe 3.5% 64.2% Intensity: no pain 38.5% mild 28.5% moderate 28.7% severe 4.3%

CDR = Clinical Dementia Rating; CPS = Cognitive Performance Scale; DBS = Discomfort Behaviour Scale; GDS = Global Deterioration Scale; Mix = AD and VaD; MMSE = Mini-Mental State Examination; NA = not available; QOL = quality of life; SD = standard deviation. * <60 years 1.5%; 61–70 years 6.9%; 71–80 years 35%; 81–90 years 47.6%; over 91 years 9.2%; ** <60 years 1.3%; 61–70 years 4.8%; 71–80 years 27.4%; 81–90 years 51.2%; over 91 years 15.4%.

Table 2. Risk of bias assessment

First author	Year	Country	Dementia subtype(s)	Sample size	Risk of bias			Selection of patients	Response	Case definition for pain	Total score
					Sampling frame	Case definition for dementia subtype	Dementia stage				
Baquero [17]	2009	Spain	AD	128	+	+	+	–	?	–	3
Bostrom [18]	2007	Sweden	AD, DLB	68	+	+	+	?	?	–	3
Buchanan [27]	2005	USA	AD	49,627	+	–	+	+	?	+	4
Colosimo [19]	2010	Italy	DLB, PSP, CBD	55	+	+	?	–	?	?	2
Hendriks [23]	2014	The Netherlands	AD, VaD, Mix, DLB	330	–	+	–	?	?	–	1
Husebo [24]	2008	Norway	AD, VaD, Mix, no dementia	181	+	+	+	–	?	+	4
Jensen-Dahm [20]	2012	Denmark	AD, Mix	321	+	+	–	–	?	–	2
Monroe [26]	2012	USA	AD, VaD, DLB	48	–	–	+	–	?	?	1
Lopez-Bastida [21] and Oliva-Moreno [22]	2006	Spain	AD	237	+	?	+	–	–	–	2
Volicer [25]	2009	The Netherlands	AD, VaD, Mix, other	929	+	–	+	–	?	–	2

Mix = AD and VaD; + = low risk of bias; – = possible risk of bias; ? = risk of bias unclear.

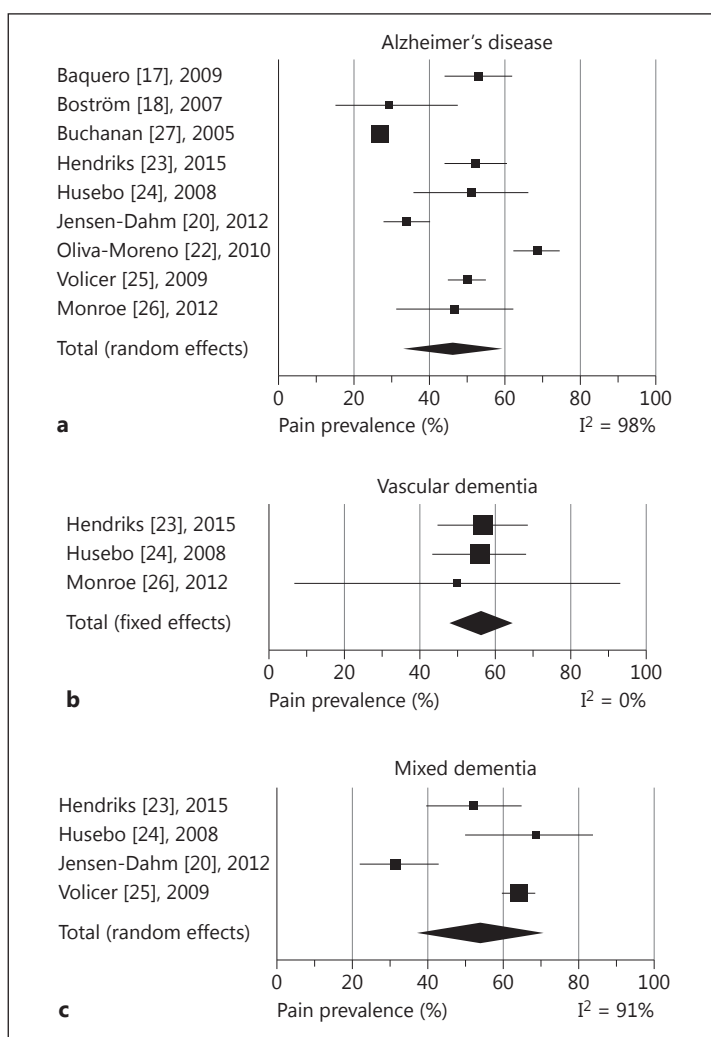


Fig. 2. Forest plot for effect of the sample-weighted pain prevalence in AD (a), VaD (b) and mixed dementia (c).

participants in LTCFs was above 80 years, and the mean age of the other participants (i.e. outpatient and community-dwelling people) was <80 years. Nine studies provided cross-sectional data on pain prevalence, one study measured pain at the end of life [26].

Prevalence of Pain in Dementia Subtypes

Nine studies reported the proportion of pain in people with AD [17, 18, 27]. Eight studies used cross-sectional data and one study reported data from a case-control study. The sample size of Alzheimer patients was 50,911, including one study with 49,627 patients, and age ranged from 48 to 103 years. The mean prevalence of pain in AD in our study was 45.8% (95% CI: 33.4–58.5%) with a substantial heterogeneity ($I^2 = 98\%$; fig. 2a).

Three studies reported on pain prevalence solely in people with VaD [22, 23]. These studies collected data on more than one dementia subtype and were based on cross-sectional data from studies carried out in LTCFs. The sample of people with VaD was a homogeneous subgroup ($I^2 = 0\%$) that consisted of 142 participants, and the mean prevalence of pain in VaD was 56.2% (95% CI: 47.7–64.4%; fig. 2b).

We found mixed dementia (AD and VaD) to be reported frequently as a separate entity next to AD and VaD, and therefore, we presented pain prevalence for mixed dementia sepa-

rately. Four studies reported on mixed dementia; three studies used cross-sectional data and one study provided data on prevalence using the baseline data of a randomized controlled trial [20, 23–25]. The sample of patients with mixed dementia was 649, and the mean prevalence of pain in mixed dementia was 53.9% (95% CI: 37.4–70.1%) with a substantial heterogeneity ($I^2 = 91\%$; fig. 2c).

Three studies reported on DLB, whereas one study combined Parkinson disease (PD) and DLB into one group. After contact with the author, it appeared that they could not be untangled. In their sample were 18 people, and nine (50%) of them suffered from pain [23]. The study by Boström et al. [18] was a case-control study that included 34 outpatients with AD and 34 outpatients with DLB. The prevalence of pain ($n = 24$) in DLB was 70% and in those with AD ($n = 32$) 30% [18]. The study by Colosimo et al. [19] collected data on nonmotor symptoms in parkinsonian syndromes, and they included 14 people with DLB, of whom seven (50%) indicated that they were in pain. We did not find enough studies to calculate a sample-weighted prevalence for DLB.

We found no studies on FTD, but we retrieved one study concerning two conditions closely related to FTD: corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) [19, 28]. Colosimo et al. [19] collected data from 11 patients with CBD and from 30 patients with PSP. Among those with CBD, 4 patients (37%) indicated that they had pain, and among those with PSP, 7 patients expressed pain (23%) [19].

Discussion

In this systematic review, we reviewed the current literature on pain in dementia to present the prevalence of pain per dementia subtype, although we found not enough studies to report a sample-weighted prevalence for each dementia subtype. We identified 10 studies that reported on pain prevalence in AD, VaD, DLB or mixed dementia (AD and VaD). We found no studies that reported on pain prevalence in FTD.

We calculated the sample-weighted prevalence, which was 45.8% (95% CI: 33.4–58.5%) for AD, 56.4% (95% CI: 47.8–64.8%) for VaD and 53.9% (95% CI: 37.4–70.1%) for mixed dementia. Our findings could not confirm the hypothesis that pain prevalence differs significantly between the different dementia subtypes.

The sample-weighted prevalence for people with AD, VaD and mixed dementia are comparable to the estimated pain prevalence of 50% that Zwakhalen et al. [29] found in their review on pain in dementia (2005); however, in their review, pain was not reported per dementia subtype. As AD, VaD and mixed dementia together account for two thirds of all dementia cases, our findings seem to be in line with those of previous studies [29, 30].

The wide range of pain prevalence might be explained by the heterogeneity in study designs, settings, patient characteristics and definition of pain. For example, in one study, pain was reported twice: one self-report and one proxy rating. As self-report is the golden standard in pain assessment [31], we decided to extract the self-reported data, but prevalence measured by self-report was lower than measured by proxy. This is in line with the findings of Scherder and van Manen [32], who found that self-reported pain in patients with AD was lower than pain observed by a nursing assistant. This may indicate that people with AD do not suffer from pain to the extent that their caregivers expect them to do or that the prevalence of pain may depend on the methods and data sources used as well as the time frame of pain detection [31, 33].

This review is not without limitations. To begin with, literature on this specific topic seems to be scarce; only 10 studies on pain in dementia subtypes fulfilled our inclusion criteria, and these studies showed substantial heterogeneity in study design. For example, prevalence of pain was usually not the main objective of the studies included in our review. In addition, we

found no studies on pain in FTD. This lack of studies could be explained by several epidemiological factors; for instance, FTD is relatively more prevalent in a younger population, whereas pain is more prevalent in the older population [4]. A specific reason for the lack of studies in DLB could be that these patients may be studied within trials assessing pain in PD, as Lewy body neuropathology is a key feature of PD and prevalence of pain in PD is estimated to be between 40 and 60% [34, 35]. Furthermore, we found that the methods of pain assessment varied widely, and many of the used instruments were not specifically designed for the population, for example the EQ-5D, which is an instrument to measure quality of life and only incorporates one pain item. We found the use of nonspecific assessment tools to be more common than the use of dementia-specific pain assessment tools. On the one hand, this was surprising, as more than 30 specific measurement instruments have been designed to measure pain especially in people with dementia [29, 36], but on the other hand, this was not surprising, as the main objectives of the included studies did not include prevalence of pain. Another limitation that should be noted is that we could not correct for the influence of comorbid pain conditions, as most of the included studies did not report comorbidity.

Our findings correspond to the previously reported prevalence of pain in people with dementia of 50%; also, our analyses showed that pain prevalence in dementia subtypes was not statistically significantly different. However, it cannot be completely ruled out that the prevalence of pain differs between the four dementia subtypes as a consequence of the differences in neuropathological changes, as we did not identify studies on pain in FTD and DLB, and we were not able to control for confounding by dementia severity and differences in pain caused by comorbidity in subtypes of dementia.

Conclusion

This is the first study that used a systematic approach to review the available literature on pain prevalence in dementia subtypes and calculated the sample-weighted prevalence of pain in patients with AD, VaD, and mixed dementia. However, we found not enough studies to calculate a sample-weighted prevalence for DLB, and we found no studies that reported on pain prevalence in FTD. The pain prevalence in FTD and DLB has not been investigated extensively, which may be due to epidemiological issues, such as the higher prevalence of AD, VaD, and mixed dementias as well as methodological issues. Whilst this study could not show a difference in pain prevalence for the different dementia subtypes, this review underlines that pain is reported frequently in people with dementia, and we recommend uniformity in pain assessment. More well-designed studies are required to draw firm conclusions on differences in prevalence of pain between dementia subtypes as a consequence of the differences in neuropathological changes. These studies should take into account comorbidity as potential confounder and focus especially on people with DLB and FTD, as both groups are underrepresented in earlier research. Research should also focus on the causes, course and characteristics of pain. Eventually, pain prevalence and its possible impact on quality of life should be a topic of future research.

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Disclosure Statement

The authors declare that they have no competing interests.

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