Clinical review

Recent developments in pain in dementia

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Epidemiological studies show that, worldwide, the number of people aged over 65 will increase substantially in the next decades and that a considerable proportion of this population will develop dementia.[1] Ample evidence shows that ageing is associated with a high rate of painful conditions, irrespective of cognitive status.[2] The number of patients with dementia who will experience painful conditions is therefore likely to increase. A key question relates to whether and how patients with dementia perceive pain. Patients with dementia may express their pain in ways that are quite different from those of elderly people without dementia.[3] Particularly in the more severe stages of dementia, therefore, the complexity and consequent (frequent) inadequacy of pain assessment leads to the undertreatment of pain.

The most commonly used pain assessment instruments seem to be selected primarily according to the communicative capacity of the patient (self report pain rating scales for communicative patients and observation scales for non-communicative patients) instead of according to two main aspects of pain—the sensory-discriminative and motivational-affective aspects. In particular, the motivational-affective aspects of pain are assessed by observation scales, which should therefore be applied to every patient, irrespective of ability to communicate. Distinction between the sensory-discriminative and motivational-affective aspects of pain is of great clinical relevance, as the motivational-affective aspects are particularly likely to reflect pain that needs treatment.[4] Moreover, differentiating between these two aspects of pain in relation to the neuropathology of the various subtypes of dementia provides insight into the basis of the alterations in the pain experiences of elderly people with dementia. Future experimental and clinical studies should not only focus on subtypes of dementia but should go a step further and assess pain in disorders in which pain is already present at a stage without cognitive impairment and during the course of which patients become cognitively impaired.

Methods

We selected data for this review from our personal files and from searches of PubMed. We used the search terms pain, chronic pain, persistent pain, acute pain, pain assessment, pain treatment, human, clinical studies, experimental studies, dementia, Alzheimer's

Summary points

Undertreatment of pain in dementia is a frequent and frightening observation; its risk increases with the severity of dementia

The development of tools by which pain can be better recognised in non-communicative patients with dementia is one of the primary goals of future research

Experimental and clinical studies should differentiate more consistently between the sensory-discriminative and motivational-affective aspects of pain and among the various subtypes of dementia

Self report pain rating scales, administered to communicative patients with dementia, focus on the intensity of pain; observation scales, until now reserved for non-communicative patients, also assess affective aspects of pain

Observation scales should become a permanent part of pain assessment, irrespective of cognitive status

Pain assessment should be a regular component of care in such disorders as Parkinson's disease and multiple sclerosis, in which pain is present at a stage in which cognitive function is relatively preserved

disease, vascular dementia, frontotemporal dementia, Parkinson's disease, and multiple sclerosis.

Undertreatment of pain in dementia

Several observational studies indicate that pain is undertreated among cognitively impaired elderly people. Fewer analgesics are prescribed for the oldest category of cancer patients (>75 years) than for younger patients, and low cognitive performance was one of the independent predictors of this finding.[5] In addition,

P+ Extra references w1-w6 are on bmj.com

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people in advanced stages of dementia who have had hip fractures receive significantly less opioid analgesics than do those who are cognitively intact.[6] Another remarkable finding is that the prevalence of use of analgesic is considerably lower among patients with Alzheimer's disease than in those with vascular dementia.[7] One possible explanation for this finding is that an impairment in language, which limits patients' ability to communicate about their pain, is more common in Alzheimer's disease than in vascular dementia.[8] These observations stress the importance of increasing our knowledge of pain recognition in this population.[3]

Assessment of the sensory-discriminative and motivational-affective aspects of pain

In clinical practice, the selection of instruments to assess pain in dementia is based primarily on whether the patient is able to communicate verbally about the pain. For example, self report pain rating scales are administered to patients who can still communicate about their pain (table 1). These scales are unidimensional, however, as they generally target only the sensory-discriminative aspects of pain (that is, presence and intensity), instead of the important motivational-affective aspects.[2] The reason these scales are used is that even patients with moderate cognitive impairment are able to use them easily to report the intensity of pain.[9–11] To assess abstract thinking, some researchers have added prerequisites for understanding, including abstract pain scales—such as the visual analogue scales, the cognitive capacity screening examination, and drawing a clock—to their protocols.[12]

Pain assessment in non-communicative patients relies primarily on observation scales (table 1).[3] Such scales may provide information about the motivational-affective aspects of pain, as shown by both physiological signs (for example, frequency of breathing) and physical signs, such as facial expressions (for example, seeming to be frightened). Facial expressions can be evaluated by a specific coding system and seem to be reliable indicators of pain.[13] One disadvantage of typical observation scales is the necessary assumption that signs that are normally indicative of pain (such as guarding, bracing, moaning) are also representative of pain in elderly patients with dementia.[14] This assumption is doubtful, however, given the identification of less obvious or atypical behavioural presentations in some people with dementia.[3] For example, "absence of a relaxed body posture," one of the items of the discomfort scale-dementia of Alzheimer type (DS-DAT), may also be a reflection of the extrapyramidal symptoms that can occur in Alzheimer's disease.[15] On the other hand, assessing for pain only with tools that include typical pain behaviours but do not recognise subtle behaviours and changes in usual activities may result in under-recognition of pain in this population.

Additional insight into a patient's pain experience could emerge from measuring such autonomic responses as blood pressure and heart rate, although evidence indicates that these measures are not particularly sensitive. In an experimental pain study, researchers observed that only high intensity pain provoked similar increases in systolic blood pressure among both patients with Alzheimer's disease and elderly people without dementia. In contrast, low intensity painful stimulation induced smaller increases in heart rate among patients with Alzheimer's disease than in elderly people without dementia.[16] These results suggest that Alzheimer's disease involves a higher threshold for autonomic activation.[16] These findings have two important clinical implications: autonomic responses in non-communicative patients may indicate a high level of pain intensity, and low autonomic responses to pain do not reflect the absence of pain. Heart rate responses to pain have recently been found to be negatively correlated with degree of cognitive impairment and deterioration of electrical activity in the brain in Alzheimer's disease, regardless of normal tactile and pain thresholds.[17] These results provide further support for the suggestion that patients with Alzheimer's disease can still differentiate between tactile and painful stimuli, even in advanced stages of the disease and in the presence of blunted autonomic responses.

Taken together, these data indicate that observation scales might be useful for assessing the intensity and motivational-affective aspects of pain in patients with dementia and that these scales should be administered to all patients, not only to those who are non-communicative as is the case in current practice. Assessing autonomic responses does not seem to be useful, as these responses do not provide an accurate reflection of the perceived intensity of pain.

Sensory-discriminative and motivational-affective aspects of pain in subtypes of dementia

The processing of sensory-discriminative aspects occurs in the lateral pain system, whereas motivational-affective aspects are processed by the medial pain system.[4] Although the distinction between these aspects of pain, and subsequently between the two pain systems, has so far received too little attention in clinical studies on pain in dementia, experimental pain studies have shown its importance.

**Table 1** Pain assessment instruments in communicative and non-communicative patients

Scale	Assessment	Aspect of pain
Most frequently used self report pain rating scales for communicative patients*		
Verbal rating scales:		
Verbal descriptor scale	Seven adjectives: no pain to most intense pain	Intensity
Verbal rating scale	Five labels, such as "distressing"	Intensity/affect
Visual rating scales:		
Visual analogue scale	No pain to most intense pain	Intensity
Faces pain scale	Seven faces expressing no pain to most intense pain	Intensity/affect
Numerical rating scales:		
Numeric rating scale	1-10 horizontal line	Intensity
21-point box scale	21 boxes: no pain to pain as bad as it could be	Intensity
Selected available observation scales for pain assessment in non-communicative patients†		
DS-DAT[w1]	Nine indicators (such as frowning)	Intensity/affect
CNPI[w2]	Six indicators (such as grimacing)	Intensity/affect
NOPPAIN[w3]	For example, pain words, pain faces, bracing	Intensity/affect
PACSLAC[w4]	Four subscales (such as facial expressions)	Intensity/affect
Doloplus 2[w5]	Three subscales: for example, somatic (such as facial) reactions	Intensity/affect

CNPI=checklist of non-verbal pain indicators; DS-DAT=discomfort scale-dementia of Alzheimer type; NOPPAIN=non-communicative patient's pain assessment instrument. PACSLAC=pain assessment checklist for seniors with limited ability to communicate.
*For comparisons of psychometric properties and more detailed description, see references 9, 11, 12, and w6.
†See www.cityofhope.org/prc/elderly.asp for a recent review of 10 observation scales, including the five observation scales presented here, that have the strongest psychometric properties.

Registration of pain related somato-sensory evoked potentials in patients with severe dementia showed that the processing of pain that involves areas of the medial pain system (such as the anterior cingulate gyrus) was impaired, although the pain stimulus itself was perceived adequately (lateral pain system).[18] Benedetti et al observed that the pain thresholds (a sensory-discriminative aspect) of patients with Alzheimer's disease did not differ from those of elderly people without dementia, whereas pain tolerance (a motivational-affective aspect) was significantly increased in the Alzheimer's disease group.[19]

The explanation of these findings is that areas that belong to the medial pain system (such as the thalamic intralaminar nuclei) and that play an important role in the motivational-affective processing of pain are severely affected in Alzheimer's disease.[20] In contrast, the primary sensory areas (the lateral pain system) are relatively preserved in Alzheimer's disease,[21] which explains the unchanged pain threshold (table 2). The lateral pain system does show some functional decline, however, as the sensory threshold was elevated in patients with Alzheimer's disease, compared with elderly people without dementia,[22] and patients with Alzheimer's disease indicated that the pain they experienced was less intense.[23] In other words, although patients with Alzheimer's disease may still perceive the presence of pain, they may experience its intensity and affective aspects to a lesser extent. Consequently, people with dementia may have difficulty understanding the meaning of the sensation and placing it in context. This could potentially explain the atypical behavioural responses observed in this population (such as frowning or fearful expressions, combativeness, withdrawal, and agitation).

In summary, with respect to Alzheimer's disease, the change in the processing of the affective components of experimental pain (higher tolerance) resembles the decrease in the motivational-affective components of clinical pain.[23] This is noteworthy, as experimental studies often use acute pain stimuli (such as electrical stimuli),[19] although most elderly people in nursing homes have persistent pain.[24] Interestingly, the incidence, severity, and duration of post-lumbar puncture headache (an acute painful condition) were found to be low in patients with dementia,[25] supporting the role of the medial pain system in processing the initial motivational-affective aspects of experimental acute pain.[26] Persistent pain is characterised by "secondary" motivational-affective aspects of pain, however, in
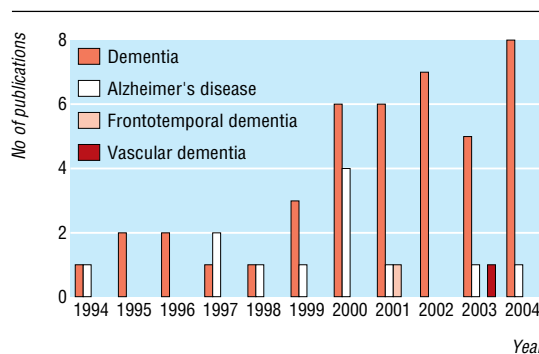
Number of clinical and experimental publications on pain in dementia, Alzheimer's disease, frontotemporal dementia, and vascular dementia between 1994 and 2004. Note that most of the papers do not distinguish the subtype of dementia

which the cognitive appraisal of the pain (for example, the future consequences of and behavioural responses to pain) plays a very important role.[27] Instruments that assess pain in dementia should therefore focus on pain related cognitive processes as well.

To date, no experimental pain studies have been conducted in other subtypes of dementia, such as vascular dementia and frontotemporal dementia. A recent review of the neuropathology of these disorders indicates that atrophy in the prefrontal cortex in frontotemporal dementia and white matter lesions in vascular dementia, in which areas become disconnected (de-afferentiation), could be responsible for the clinically observed respective decrease and increase in the motivational-affective aspects of pain (table 2).[28] The difference in pain experience between subtypes of dementia underscores that studies on pain should not focus solely on the general definitions of "cognitively impaired elderly people" or "elderly people with dementia." A systematic key word search of PubMed, however, shows that such broad diagnoses were still used in most pain studies in the past decade (1994-2004) (figure).

Future

In disorders with a high risk of cognitive impairment, such as Parkinson's disease and multiple sclerosis, pain is a prominent clinical symptom at a stage in which patients' cognitive status is relatively preserved.[29 30] Pain syndromes that often occur in these patients include

Table 2 Relation between neuropathology and results of experimental and clinical studies with respect to influence of subtypes of dementia, and the influence of Parkinson's disease and multiple sclerosis without cognitive impairment, on motivational-affective aspects and presence or intensity of pain

Condition	Motivational-affective aspects of pain		Presence or intensity of pain	
	Possible neuropathological involvement	Experimental and clinical results	Possible neuropathological involvement	Experimental and clinical results
Alzheimer's disease	Degeneration of thalamic intralaminar nuclei	↓	Relatively unaffected	Relatively unaffected
Vascular dementia	De-afferentiation	↑	Not examined	Not examined
Frontotemporal dementia	Degeneration of prefrontal cortex	↓	Not examined	Not examined
Parkinson's disease, not cognitively impaired	Degeneration of brain stem nuclei	↑	Relatively unaffected	Not examined
Multiple sclerosis, not cognitively impaired	De-afferentiation	↑	Dysfunction of spinothalamic tract	↓

trigeminal neuralgia, pain related to spasticity and rigidity, radicular-neuropathic disorders, and central pain.[29] [30] To date, the relation between the site of the neuropathology (such as cortical atrophy or white matter lesions) and pain experience has received little attention in these disorders. Depending on the location of the neuropathology, degeneration of the various brain stem areas (such as the locus coeruleus) that are normally involved in the inhibition of nociceptive stimuli at the spinal dorsal horn could hypothetically explain the clinically observed increase in the motivational-affective aspects of pain in Parkinson's disease.[31] The sensory-discriminative aspects have yet to be clinically examined in Parkinson's disease (table 2). As in vascular dementia, de-afferentiation by white matter lesions may explain the increase in affective-emotional pain in multiple sclerosis. Furthermore, reductions have been observed in pain-temperature sensation (a sensory-discriminative aspect), possibly as a result of a dysfunction of the spinothalamic tract (table 2).[32]

Because some of these patients inevitably develop cognitive impairments during the course of their disease, it is alarming to realise that the experience of pain and all of its aspects during this stage remain to be examined. This lack of knowledge hampers the development of effective pain treatment strategies with respect to not only the painful conditions in the cognitively impaired stage but also the side effects of drugs in Parkinson's disease and multiple sclerosis. For example, in Parkinson's disease, levodopa can provoke pain and burning paraesthesia,[33] and an increase in pain has been observed when using interferon beta in multiple sclerosis.[29] The extent to which these side effects are influenced by alterations in cognitive impairment is unknown. These examples illustrate that people who care for elderly patients should be alert to pain at all stages of neurodegenerative disorders, irrespective of a patient's cognitive status.

In the coming decade, this line of research should progress, particularly if researchers differentiate among the various aspects of pain and pay attention to the various subtypes of dementia and the stage of the neurodegenerative disorder. The role of pain in diseases that can cause cognitive impairment, such as Parkinson's disease and multiple sclerosis, must be incorporated into future experimental and clinical pain studies.

1 Skoog I. Psychiatric epidemiology of old age: the H70 study—the NAPE lecture 2003. *Acta Psychiatr Scand* 2004;109:4-18.
2 Horgas AL, Elliott AF. Pain assessment and management in persons with dementia. *Nurs Clin North Am* 2004;39:593-606.
3 Herr K, Decker S. Assessment of pain in older adults with severe cognitive impairment. *Ann Long Term Care* 2004;12:46-52.
4 Sewards TV, Sewards MA. The medial pain system: neural representations of the motivational aspect of pain. *Brain Res Bull* 2002;59:163-80.
5 Bernabei R, Gambassi G, Lapane K, Landi F, Gatsoni C, Dunlop R, et al. Management of pain in elderly patients with cancer. *JAMA* 1998;279:1877-82.
6 Morrison RS, Siu AL. A comparison of pain and its treatment in advanced dementia and cognitively intact patients with a hip fracture. *J Pain Symptom Manage* 2000;19:240-8.
7 Semla TP, Cohen D, Paveza G, Eisdorfer C, Gorelick P, Luchins D, et al. Drug use patterns of persons with Alzheimer's disease and related disorders living in the community. *J Am Geriatr Soc* 1993;41:408-13.
8 Lindeboom J, Weinstein HC. Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. *Eur J Pharmacol* 2004;490:83-6.
9 Ferrell BA, Ferrell BR, Rivera L. Pain in cognitively impaired nursing home patients. *J Pain Symptom Manage* 1995;10:591-8.
10 Scherder EJA, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. *Gerontology* 2000;46:47-53.
11 Closs SJ, Barr B, Briggs M, Cash K, Seers K. A comparison of five pain assessment scales for nursing home residents with varying degrees of cognitive impairment. *J Pain Symptom Manage* 2004;27:196-205.
12 Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. *Clin J Pain* 2004;20:207-19.
13 Hadjistavropoulos T, LaChapele DL, Hadjistavropoulos HD, Green S, Asmundson GJG. Using facial expressions to assess musculoskeletal pain in older persons. *Eur J Pain* 2002;6:179-87.
14 Kovach CR, Weissman DE, Griffie J, Matson S, Muchka S. Assessment and treatment of discomfort for people with late-stage dementia. *J Pain Symptom Manage* 1999;18:412-9.
15 Caligiuri MP, Peavy G, Galasko DR. Extrapyramidal signs and cognitive abilities in Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;16:907-11.
16 Rainero I, Vighetti S, Bergamasco B, Pinessi L, Benedetti F. Autonomic responses and pain perception in Alzheimer's disease. *Eur J Pain* 2000;4:267-74.
17 Benedetti F, Arduino C, Vighetti S, Asteggiano G, Tarenzi L, Rainero I. Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration. *Pain* 2004;111:22-9.
18 Yamamoto M, Kachi T, Igata A. Pain-related somatosensory evoked potentials in dementia. *J Neurol Sci* 1996;137:117-9.
19 Benedetti F, Vighetti S, Ricco C, Lagna E, Bergamasco B, Pinessi L, et al. Pain threshold and pain tolerance in Alzheimer's disease. *Pain* 1999;80:377-82.
20 Rüb U, Del Tredici K, Del Turco D, Braak H. The intralaminar nuclei assigned to the medial pain system and other components of this system are early and progressively affected by Alzheimer's disease-related cytoskeletal pathology. *J Chem Neuroanat* 2002;23:279-90.
21 Dickson DW. Neuropathology of Alzheimer's disease and other dementias. *Clin Geriatr Med* 2001;17:209-28.
22 Gibson SJ, Voukelatos X, Ames D, Flicker L, Helme RD. An examination of pain perception and cerebral event-related potentials following carbon dioxide laser stimulation in patients with Alzheimer's disease and age-matched control volunteers. *Pain Res Manage* 2001;6:126-32.
23 Scherder EJA, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. *Gerontology* 2000;46:47-53.
24 Helme RD, Gibson SJ. The epidemiology of pain in elderly people. *Clin Geriatr Med* 2001;17:417-31.
25 Blennow K, Wallin A, Häger O. Low frequency of post-lumbar puncture headache in demented patients. *Acta Neurol Scand* 1993;88:221-3.
26 Créac'h C, Henry P, Caillé J-M, Allard M. Functional MR imaging analysis of pain-related brain activation after acute mechanical stimulation. *Am J Neuroradiol* 2000;21:1402-6.
27 Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000;288:1769-72.
28 Scherder EJA, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol* 2003;2:677-86.
29 Bacher Svendsen K, Staehelin Jensen T, Overvad K, Hansen HJ, Koch-Henriksen N, Bach FW. Pain in patients with multiple sclerosis: a population-based study. *Arch Neurol* 2003;60:1089-94.
30 Waseem S, Gwinn-Hardy K. Pain in Parkinson's disease: common yet seldom recognized symptom is treatable. *Postgrad Med* 2001;110:33-46.
31 Braak H, Rüb U, Sandmann-Keil D, Gai WP, de Vos RAI, Jansen Steur ENH, et al. Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. *Acta Neuropathol* 2000;99:489-95.
32 Kakigi R, Kuroda Y, Neshige R, Endo C, Shibasaki H. Physiological study of the spinothalamic tract conduction in multiple sclerosis. *J Neurol Sci* 1992;107:205-9.
33 Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. *Neurology* 1976;34:957-9.

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Endpiece

The ideal diagnosis

One finger in the throat and one in the rectum makes a good diagnostician.

Sir William Osler (1849-1919), Canadian born British physician and educator

Fred Charatan, retired geriatric physician, Florida