Assessment and Management of Pain in Patients with Dementia

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Christina Jensen-Dahm

Abbreviations

AD	Alzheimer's disease
CNS	Central nervous system
DLB	Dementia with Lewy Bodies
FTD	Frontotemporal Dementia
MMSE	Minimental state examination
NSAID	Non-steroidal anti-inflammatory drug
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PAINAD	Pain in Advanced Dementia
WHO	World Health Organization

Introduction

Pain is defined by the International Association for Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. It is classified as acute—associated with trauma or injury—or chronic (lasting longer than 3 months). Pain perception is a subjective and complex experience, which involves sensory-discriminative components (i.e., location, intensity, duration), affective-motivational (e.g., unpleasantness of the noxious stimuli), and cognitive components. The prevalence of pain rises with increasing age [2, 3], and likewise does the incidence of dementia. Thus, it

C. Jensen-Dahm (✉)
Danish Dementia Research Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
e-mail: christina.jensen-dahm@regionh.dk

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must be expected that a considerable number of patients experience both pain and dementia.

Any cognitive disorder, in which deficits in memory and reasoning are cardinal symptoms, could be expected to have a profound effect on an individual's appraisal of the pain experience and its future implications. In judging pain severity, we rely on previous experiences and knowledge of pain, underpinned by episodic memory and semantic memory. Memory problems may lead to patients forgetting that they experienced pain recently and therefore not communicating they were in pain. Likewise, aphasia could lead to problems expressing pain. Lack of insight may also mean that patients with dementia fail to report pain when consulting a physician. In terms of pain assessment dementia is a double-edged sword. Pain affects cognitive function [4], and cognitive function also affects pain assessment as patient's report still is the primary mean for pain assessment [5, 6].

Pain in the Elderly

The prevalence of pain in the elderly population in general is difficult to estimate and has varied from 0 to 93% depending on the population and definition of pain [7]. The prevalence of pain rises with increasing age, though some studies have found that it reaches a plateau after age 65 [7, 8]. The prevalence of chronic pain is estimated to be 20–25% in men over the age of 65 and 30–35% in women over the age of 65 [9, 10]. The most frequent causes of pain in the elderly are related to osteoarthritis, especially in the back and neck, which is present in up to 65% of elderly with chronic pain. Other frequent causes are musculoskeletal problems (40%), neuropathic pain (35%), and chronic joint pain (15–25%) [8]. Elderly patients with musculoskeletal pain often have pain from several regions. Likewise, the elderly with chronic pain often have different pain-causing conditions. Older people with dementia have worse overall oral health than older people without dementia, including coronal caries, root caries, and retained roots [11]. Orofacial pain and its potential causes were frequently present in elderly with dementia [11, 12] and more so than in elderly without dementia [11]. Furthermore, one study found a correlation between the severity of cognitive impairment and potential painful oral conditions [12].

Epidemiology of Pain in Dementia

Knowledge about the epidemiology of pain in patients with dementia is to a large extent, based on studies of nursing home residents. A review of studies published between 1999 and 2009 found that pain prevalence among nursing home residents varied between 3.7 and 79.5% depending on the method used [13]. In a large study of almost 10,000 nursing home residents, a negative association between dementia and pain was observed [14]. This was supported by a study that observed that increasing degree of cognitive impairment leads to lower frequencies of observed pain among nursing home residents [15]. However, both studies were based on

observer ratings (minimum dataset), and one may speculate whether the lower frequency of pain was due to communication problems, leading to undiagnosed pain. An alternative explanation may be that patients with and without dementia were admitted to a nursing home for different reasons, i.e., patients with dementia were living in a nursing home due to cognitive impairment, whereas the cognitively intact were living at nursing homes due to severe illness or disability and therefore were more likely to suffer from pain.

Few studies have investigated prevalence of pain in community-dwelling patients with dementia. A Finnish population-based study of elderly over 75 years found that the prevalence of pain was significantly lower in patients with dementia. This was irrespective of whether they evaluated pain during the preceding month, presence of daily pain, pain interfering with routine activities, or daily pain at rest. The findings did not seem to depend on the degree of dementia, though patients were mainly suffering from mild to moderate dementia [16]. In contrast, results from the "Swedish National Study of Aging and Care—Kungsholmen" found a similar prevalence of pain in home-living patients with dementia compared to those without dementia [17]. Thirty-five percent of nursing home residents without dementia were reporting pain in contrast to 8.6% of nursing home residents with dementia. However, 48.9% of nursing home residents with dementia were unable to answer the question, and this may point toward one obvious mechanism behind the epidemiological finding of a lower prevalence of pain in patients with dementia, i.e., problems with communicating pain.

The majority of studies have not distinguished between different types of dementia when assessing pain prevalence or pain report. The studies that have focused on subtypes of dementia have mainly focused on Alzheimer's disease, and a few have focused on vascular dementia and/or mixed dementia. At present, there is limited evidence about pain prevalence in dementia with Lewy bodies and frontotemporal dementia [18].

Alzheimer's Disease

In 1997 Fisher-Morris and Gellatly published a report of two patients with Alzheimer's disease (AD), where they had observed a marked decrease in pain responses. The first case was a 90-year-old woman with a fungating carcinoma of the breast, which ulcerated through the skin and destroyed the breast and chest wall. During the 18 month the patient lived in a nursing home, her response to the lesions was gradually diminished, and she did not complain of pain. The second case was a 70-year-old man with AD, who sustained a femur fracture, but still walked around without complaining of pain, which lead the authors to speculate if AD leads to a change in pain perception [19].

A reduced report of pain is supported by a study comparing pain intensity ratings in cognitively intact elderly and patients with early and moderate AD matched for painful conditions, which showed that cognitively intact peers rated pain significantly higher than patients with AD. The study also found a correlation between pain intensity and stage of AD, as patients with early AD rated pain higher than

patients with moderate AD [20]. In a similar study, the same authors were able to show that patients with early AD reported lower pain scores on a visual analog scale and lower affective distress associated with pain compared to the cognitively intact [21]. The same authors found that the patients experienced less pain during activities of daily living, and pain had a lower impact on daily life than controls. Similar in a study examining patient's and proxy's ratings of pain in 321 patients with early AD using part of a self-rated health scale (EQ-5D), it was found that 32.9% of the patients reported pain, whereas 51.4% of their caregivers judged the patients to experience pain. The authors compared the finding to EQ-5D norms for the elderly Danish population, in which approximately 50% reported pain, which was considerably higher than in patients with early AD [22]. In a recent study of pain complaints in outpatient memory clinic patients, it was found that elderly with AD complained significantly less than elderly with subjective cognitive impairment [23]. The exact prevalence of pain varies considerably from study to study depending on the sample and what is measured (any pain, daily pain, chronic pain, etc.). A systematic recent review found that the pain sample-weighted pain prevalence was 45.8% (95% CI: 33.4–58.5%) for AD [18].

Other Types of Dementia

To date, there have been no studies examining the prevalence of pain in frontotemporal dementia (FTD). There is very limited evidence about dementia with Lewy bodies (DLB). In Parkinson's disease pain is frequent and is a frequent pre-motor symptom [24], but if this the case in DLB is not known. Studies have shown that nursing home patients with "possible" or "probable" vascular dementia were more likely to self-report pain [25], more likely to suffer from chronic pain [26], and reported higher pain intensity than nursing home residents without dementia [27]. Furthermore, more pain locations were observed in patients with vascular dementia and mixed dementia compared to AD [28]. A recent study found a positive relationship between white matter hyperintensities and self-reported pain intensity in older patients with and without dementia [29]. However, a recent systematic review found no differences in pain prevalence among dementia subtypes, although limited data about vascular dementia [18].

Pathophysiology of Pain in Dementia

Supraspinal Mechanism of Pain

Pain is the psychophysiological result of an unpleasant internal or external stimulus, which activates a group of receptors called nociceptors. Nociceptors are located in the skin, and other tissues (first-order neurons) and information is projected to the dorsal horn of the spinal cord (second-order neurons) [30]. From the spinal cord, the information is transmitted via the spinoreticular, spinomesencephalic, and spinothalamic tract to the brain stem and thalamus. Areas of the brain stem such as the periaqueductal gray, rostral ventromedial medulla, and locus coeruleus are important

sites for pain modulating systems and constitute part of a descending modulatory pain system [30]. From the brain stem information is transmitted to the spinal cord and the central nervous system (CNS) (third-order neurons). The thalamus, located within the diencephalon, is the major relay station for sensory information projected to the CNS.

Pain perception is a complex experience, which involves sensory-discriminative components (i.e., location, intensity, duration), affective-motivational (e.g., unpleasantness of the noxious stimuli), and cognitive components. It has been suggested that the sensory-discriminative and affective-motivational components of pain are largely represented by separate pathways that target lateral and medial nuclei of the dorsal thalamus [30–33].

The spinothalamic tracts have their main targets in the lateral thalamic nuclei (ventral posterolateral, ventral posteromedial and ventral posterior inferior nuclei), which project to the contralateral primary sensory cortex, secondary somatosensory cortex, parietal operculum, and the mid- and posterior part of the insula also referred to as the lateral pain pathway. The lateral pain pathway encodes sensory-discriminative aspects of pain, i.e., spatial localization and intensity of painful stimuli [30, 31]. This is supported by the clinical finding that patients with lesions in the primary and secondary sensory cortices have deficits in pain sensations and disturbed ability to localize pain [34]. However, lesions at different levels of the somatosensory pathway can lead to central pain, which can occur in stroke patients [35].

The medial thalamic nuclei (central median nucleus and intralaminar complex) projects to structures of the limbic system (anterior cingulate cortex, amygdala, hippocampus, insula, and prefrontal cortex) and is thought to process the affective-motivational and cognitive components of pain [36, 37], also referred to as the medial pathway [30–33]. The anterior cingulate cortex has been shown to be important for the affective-motivational and cognitive aspects of pain [33, 38]. Connections between the anterior cingulate cortex, prefrontal cortex, and periaqueductal gray and connections between insula, amygdala, and periaqueductal gray constitutes part of the descending pain modulatory pathways [30, 37].

Pathological Changes in Alzheimer's and Pain Processing

The pathological changes in AD patients develop over decades. Coinciding with the diagnosis of AD, the patients have widespread changes of the limbic system with interruption of connections between components of the limbic system, and its influence on the prefrontal cortex is markedly reduced (equivalent to Braak stage IV–V) [39, 40]. At stage V, there are widespread changes of the neocortex, but the primary motor and sensory cortex remain largely unaffected until the severe stages of AD (stage VI). The pathological changes in AD have a wide impact on the limbic system, which plays an important role in processing the "affective-motivational" component of pain. Furthermore, patients with AD have pathological changes in the intralaminar and medical nuclei of the thalamus, which are progressively affected by the disease, with severe changes in pathological stages equivalent to clinical AD [41]. The relative sparing of the sensory cortex and the impact on the limbic system

and medial thalamic nuclei led Scherder et al. to conclude that the pathological changes in AD have a wide impact on the medial pain system [42], but the lateral system (sensory-discriminative aspects) are largely unaffected. However, at severe stages of AD amyloid plaques have been found in almost all thalamic nuclei [43].

Pathological alterations have also been found in areas of the brain stem, with evidence of neuronal loss in the locus coeruleus [44], parabrachial region [41, 45] and in the periaqueductal gray matter [46], which are important for modulating pain. Thus, AD pathology affects several areas of the brain important for processing and modulating pain.

Pathological Changes in Other Types of Dementia

Vascular dementia is a heterogenous disorder, and because infarctions of the brain can occur at many locations, all areas involved in pain processing can potentially be affected. Disruption of connections in the cortex and between the cortex and subcortex by white matter lesions may theoretically increase the experience of pain in vascular dementia [42], and white matter hyperintensities have also been associated with increased self-reported pain in patients with dementia [29]. Furthermore, there is an increased risk of post-stroke central pain [35]. In frontotemporal dementia, there can be atrophy of part of the medial pain system such as the prefrontal gyrus, the insula, and the anterior cingulate cortex. Thus, theoretically patients with FTD may have a change in pain perception [42, 47], but clinical date about pain in FTD is missing making it difficult to judge potential effects of neuropathology. In Parkinson's disease, there is Lewy body pathology in areas of the brainstem important for pain processing such periaqueductal gray and locus coeruleus [24], but this have not been specifically assessed in dementia with Lewy bodies.

Evidence from Experimental Pain Studies

A number of experimental studies have investigated the effect that dementia have on pain processing. To date, the majority of studies have focused on AD or mixed groups of patients.

Experimental studies have investigated the hypothesis that AD leads to a change in pain processing and thus, in pain experience. The sensory-discriminative aspects of pain can be studied by investigating the pain threshold. Consistent with the neuropathological finding that the sensory cortex remains intact until late in the disease, the majority of studies have found that the pain threshold (a measure of the sensory-discriminative component of pain) was intact [48–54]. The affective-emotional aspect of pain can be studied by investigating pain tolerance, where results have been differing [49], but with the majority pointing toward a decrease in pain tolerance in mild to moderate AD [51, 52].

A few studies have assessed motor, facial, and brain responses to experimentally induced pain. Here, the picture tends to look more consistent with most findings pointing to a somewhat augmented processing of nociceptive

information in patients with AD. More precisely, it was found that patients with dementia showed increased facial responses to pain compared to healthy individuals [53, 55, 56]. Importantly, this increase was not accompanied by an overall increase in facial responsiveness (e.g., unspecific grimacing) but was solely due to an augmentation of pain-specific facial expressions. Regarding brain responses, supraspinal processing of nociceptive inputs in patients with AD has only been investigated in a few studies. Despite the hypothesis of impaired pain pathway in AD patients, functional brain imaging studies (fMRI) show that brain activity in response to noxious stimulation is preserved and even elevated in both the medial and lateral pathways [57, 58]. Interestingly, these studies also observed prolonged activation in the pain pathways and increased activity in cognitive regions, such as the dorsolateral prefrontal cortex. This suggests that cognitive integration of pain may be altered in elderly with AD and could also suggest that they experience greater distress than those without dementia. Thus, taken together, the lower frequency of self-reported pain in AD cannot be explained by impaired processing due to selective impairment of the affective-motivational or cognitive component of pain, suggesting that pain is not less frequent and intense even if no longer reported.

Observation and Assessment of Pain in Dementia

General Assessment of Pain in the Elderly

Assessment of pain requires a comprehensive assessment across all populations and should include a detailed investigation of a patient's pain and medical history, a physical examination, and diagnostic testing if needed. A pain history should include characterization of the current complaint, including associated features or secondary signs and symptoms. The present pain complaint should be described in terms of intensity, quality, location(s) (including radiation), pattern (including onset, duration, and frequency), and aggravating and relieving factors and consequences [7, 8, 59–61]. Nonverbal cues (e.g., guarding, grimacing, and restricted movement) should be noted, particularly if the older person is unable to provide a description of the pain, and furthermore, in circumstances where self-report is unobtainable, gathering information and history from other sources, such as the primary caregiver, can be helpful [60, 62–64]. One of the main purposes of the history and physical exam is to identify a cause of pain. Older adults typically present with multiple pain etiologies. Indeed, a comprehensive assessment is even more critical in this population, in order to gather complete information on all of the locations of pain and the types of conditions that may be causing pain.

Mild to Moderate Dementia

Assessment of pain gets increasingly difficult with the increasing severity of dementia. Studies investigating the capacity of patients with dementia to self-report pain

have shown that this ability declines across the course of dementia [20, 21, 65–67]. One study examined the ability of elderly with dementia to understand and use four standard pain assessment scales in different stages of dementia ((1) Horizontal visual analog scale, which consists of a 10-cm line anchored by two extremes of pain: no pain and extreme pain; (2) Vertical visual analog scale is similar to the prior scale but is presented vertically; (3) The faces pain scale consists of a drawing of seven faces that express increasing pain; (4) The 6-point verbal rating scale consists of a list of adjectives which describe different levels of pain) [65]. The study found that in patient with mild dementia 97% were able to understand and use at least one scale and 80% understood all four scales. In patients with moderate dementia 90% understood at least one scale and 59% understood all four scales. There was a high-reliability and correlation between scales. Patients with dementia had the most difficulty using the Faces Pain Scale. Thus, according to published guidelines self-reporting of pain is the standard gold method for identifying pain in those with mild to moderate cognitive impairment [7, 63, 68]. It is recommended to use the numerical rating scale or verbal descriptors with categories of a degree of pain (such as "no pain," "mild pain," "moderate pain," "severe pain," and "worst pain imaginable"). If using a visual analog scale, it is recommended to use a vertical visual analog scale and preferably a colored visual analog scale. The Faces Pain Scale has been shown to be the most difficult to use and is not recommended [20, 65, 66]. People with moderate to severe communication problems should be offered additional assistance with self-report, and the health care provider may need to try different measures.

Severe Dementia

Assessment of pain poses the greatest challenges in cases of severe dementia. The ability to self-report pain has been examined in elderly with severe dementia. In a study of the ability to use and comprehend standard pain assessment scales (Horizontal visual analog scale, Verbal rating scale, and Faces Pain Scale, see previously for description) in patients with severe dementia, it was found that 60% were able to understand at least one of the three scales and even in those with an mini-mental state examination (MMSE) below 6 50% demonstrated comprehension of at least one scale [66]. In patients who demonstrated good comprehension, the reliability of the three self-assessment scales was good. Thus, when people with severe cognitive impairment can self-report pain, these reports are valid [68]. It is important to try to achieve a self-report of pain from all patients, even if the patient can only confirm that they are in pain, as self-report is the gold-standard [64] and the only way to be certain that the patient has pain. If a patient answer "yes" to the question it is important to check that the individual understood the question and does not reply "yes" to every question asked. In patients with moderate to severe communication problems additional assistance needs to be provided and different measures used to achieve self-report [60, 63, 68].

In cases with severe communication difficulties and in situations where a procedure can cause pain, an observational assessment of pain behavior is

additionally required and is a valid approach [60, 63]. Patients with dementia, who have difficulty communicating, may express pain by a change in behavior. The American Geriatric Society has defined a number of common behaviors that may indicate pain [63], please see Table 9.1. Some behaviors are common and typically considered to be pain related (e.g., facial grimacing, moaning, groaning, rubbing a body part), but others are less obvious (e.g., agitation, restlessness, irritability, confusion, combativeness particularly with care, changes in appetite or

Table 9.1 Observational changes associated with pain and alternative explanations

Type	Symptoms	Alternative explanations
Autonomic changes	Pale, sweating, tachypnea, change in breathing, increase in pulse and/or blood pressure	Infection, worsening of chronic obstructive pulmonary disorder, pulmonary edema, heart disease
Facial expression	Slight frown; sad, frightened face Grimacing, wrinkled forehead, closed, or tightened eyes Any distorted expression Rapid blinking	Distress associated with the situation Psychosocial circumstances, for instance, problematic social relations at the nursing home
Body movements	Rigid, tense body posture, guarding Fidgeting Increased pacing, rocking Restricted movement Gait or mobility changes	Neuropsychiatric symptoms. Parkinsonism Side effect to antipsychotic Bad fitting shoes
Verbalizations/ vocalizations	Sighing, moaning, groaning Grunting, chanting, calling out Noisy breathing Asking for help Verbally abusive	Neuropsychiatric symptoms Psychosocial circumstances, for instance, problematic social relations at the nursing home Lung disease
Changes in interpersonal interactions	Aggressive, combative, resisting care Decreased social interactions Socially inappropriate, disruptive Withdrawn	Psychosocial circumstances, for instance, problematic social relations at the nursing home Depression Neuropsychiatric symptoms
Changes in activity patterns	Refusing food, appetite change Increase in rest periods Sleep, rest pattern changes Sudden cessation of common routines Increased wandering	Psychosocial circumstances, for instance, problematic social relations at the nursing home Depression Infection
Mental status changes	Crying or tears Increased confusion Distress or irritability	Psychosocial circumstances, for instance, problematic social relations at the nursing home Depression Medication side effects Neuropsychiatric symptoms

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usual activities) [64]. Typical pain behaviors may not be present, and more subtle indicators may be the only indicator of unrecognized pain. Unusual behavior in a patient with severe dementia should trigger assessment for pain as a potential cause. Furthermore, if pain is suspected, it is important to investigate the cause of pain as it may be due to serious underlying disease. Pain behaviors are not specific reflections of pain and can be caused many underlying causes of which pain is one, but also other sources of distress, such as physiologic or emotional distress [62, 64, 69]. Pain behaviors differ between individuals, so assessment should include insights from familiar caregivers and family members to interpret the meaning of their behaviors. Box 9.1 shows an algorithm for assessment of pain in patients with dementia [60–64, 68, 70].

Box 9.1 Algorithm for Assessment of Pain in Elderly with Dementia

1. *Is the patient able to communicate sufficiently?*
   (a) If no, continue to 2.
   (b) If yes, ask the patient if he/she is in pain. Use alternate words such as sore, ache, discomfort, or agony. Try to get a detailed pain history. Treat the cause of pain or the pain.
2. *Use observations from caregivers or relatives familiar with the patient.*
3. *Observe for potential pain indicators, assess changes in the following*:
   (a) Autonomic changes
   (b) Facials expression
   (c) Body movement/language
   (d) Verbalizations
   (e) Changes in interpersonal interactions
   (f) Change in activity patterns
   (g) Mental status changes
4. *If potential "pain indicators" are observed ask the following questions to examine what the behavior means*:
   (a) Are basic need fulfilled, i.e., thirst, hunger, need for visiting the toilet, hearing or visual aid?
      (i) If not, correct this. If it does not help, continue the search.
   (b) Are behavior present during movement/transfer?
      (i) If yes, consider strategies to prevent movements that induce pain, provide reassurance and/or consider premedication before provocative movements.
   (c) Are there evidence of morbidity which may cause pain?
      (i) Examine for the potential disease which may cause pain such as pressure ulcers, constipation, or infection among others.
5. *Consider analgesic trial. Monitor response carefully and plan for close follow-up.*
6. *If behavior persist, search for alternative causes by involving caregivers or relatives familiars with the patient*

Pain Assessment Scales

Pain assessment scales can be used to recognize behavior, which may indicate pain and can be used as a proxy for the presence of pain. Most of the instruments are based on the assumption and recommendations of the American Geriatrics Society Panel that pain can be expressed by changes in facial expression (e.g., frowning), vocalization and verbalization (e.g., groaning, mumbling), and body movements [59, 63]. A large number of scales have been developed and aim to make a systematic approach to observe pain behavior in the elderly with dementia [64]. In 2014 28 different scales had been developed to assess pain in different situations and groups of patients. For all 28 scales, there is limited evidence about their reliability, validity, and clinical utility [71]. The interpretation of many of these behaviors is complex when applied to dementia due to considerable overlap with other common behavioral symptoms or cognitive deficits which may confound an assessment, manifesting from boredom, hunger, anxiety, depression, or disorientation [72]. This increases the complexity of identifying the presence of pain accurately in patients with dementia. Generally, none of the scales are specific for pain and measure other sources of distress as well. Importantly, most scales are validated for ascertaining the presence of pain, but not the pain intensity. In most scales, we do not know if scoring a higher number of behavioral items also means more pain [72]. It is important that the pain assessment is not the sole measure but are used to identify patients who may have pain as a part of a comprehensive pain assessment [7, 60, 62, 64, 72].

In the British Geriatric Societies guideline from 2018, they highlight three pain scales: (1) Pain in Advanced Dementia (PAINAD), (2) Doloplus-2 and (3) Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC). PAINAD assesses five domains (breathing, negative vocalization, facial expression, body language, and consolability) from 0 to 2 points (max score of 10). It is a sensitive tool for detecting pain in adults with dementia, but does have a high false-positive rate [73]. The scale has not been evaluated in adults with mild to moderate dementia. PAINAD has a high sensitivity (92%) but low specificity for pain (62%). It is easy and simple to use [74]. Doloplus-2 assesses somatic reactions (5 domains), psychomotor reactions (2 domains), and psychosocial reaction (3 domains), which are graded from 0 to 3, yielding a max score of 30 [66, 75, 76]. Doloplus-2 has been translated into many languages, including English, for use across Europe. The PACSLAC consists of four subscales: facial expression, activity/body movement, social/personality mood, and others. Each sub-scale is scored, and a total score is generated. The PACSLAC scale has good inter-rater reliability [77–79], but does need a short form and more testing in larger scale studies.

Treatment of Pain in Dementia

General Principles of Pain Treatment

Treatment of pain in elderly with dementia follows the same guidelines as for elderly without dementia, and for an extensive review we refer to designated texts [7, 8, 59, 80–85].

With age, a number of physiological changes occur, which affect the ability to handle drugs, and these changes need to be kept in mind [59, 86, 87], see Table 9.2 for a summary. Physiological changes in older people increase the sensitivity to some analgesic drugs, resulting in them being more susceptible to side effects and sometimes requiring lower doses. Thus, in choosing analgesics, comorbidity and interactions with other medication need to be taken into account in order to reduce the chance of drug–disease and drug–drug interactions [7, 59, 80]. Especially in frail, multimorbid patients, it is important to preserve function and avoid treatment-related morbidities such as falls, confusion, and delirium [82].

Only one drug should be initiated at a time using a low dose, and this should be followed by slow dose titration, using the principle "start low and go slow." Sufficiently long intervals between introducing drugs should be allowed to assess the effect. Analgesics should, however, always be titrated to response or alternatively discontinued because of side effects and insufficient effect. The least invasive route of administration should be preferred, and subcutaneous formulations reserved for patients with dysphagia [84]. Timing of medication administration is important. Severe, episodic pain requires treatment with medicines with a rapid onset of action and short duration. However, if a patient is experiencing continuous pain, regular analgesics are the most effective, possibly using modified release formulations. Treatment should be constantly monitored and adjusted if required to improve

Table 9.2 Pharmacological changes with aging

Pharmacological function	Change with normal aging	Common effect of disease
Gastrointestinal absorption and function	Increased gastrointestinal transit time may increase the risk of opioid-related obstipation	Change in gastric PH may alter the absorption of drugs
Transdermal absorption	Usually no age-related changes	Increase in body temperature may increase absorption from patches
Distribution	Increased fat/muscle ratio may increase volume for distribution of fat-soluble drugs	Aging and obesity may increase the distribution of fat-soluble drugs, which result in longer effective drug half-life
Liver metabolism	Pre-, intra, and post-hepatic age-related changes may lead to a decrease in conjugation, metabolism, and clearance of drugs. The exact effect can be difficult to predict	Cirrhosis may change metabolism and clearance of drugs
Renal excretion	Glomerular filtration rates decreased with advancing age which leads to a decrease in clearance and excretion of drugs and metabolites, leading to the prolonged half-life of drugs	Chronic kidney disease may predispose to renal toxicity and accumulation of drugs leading to systemic toxicity
Anticholinergic side effects	Increased confusion, constipation, incontinence, and movement disorders	Enhanced by neurological disease

efficacy and limit adverse events. Combination therapy using drugs with complementary mechanisms of action may have synergistic effects to provide greater pain relief with fewer side effects than higher doses of a single drug [7, 59, 80]. However, in patients receiving polypharmacy, this may decrease compliance. Treatment of pain should follow a step-wise approach following the World Health Organization (WHO) analgesic ladder [88]. When starting an analgesic, a plan for follow-up with evaluation of effect and side effects should be made. At every follow-up, discontinuation of analgesics should be considered [89].

Paracetamol

Paracetamol is first-choice due to a favorable side effect profile [7, 8, 47, 80, 90]. It is effective towards musculoskeletal pain. Paracetamol is relatively safe and without significant side effects. It is important that the dose is not increased beyond the maximum dose of 4 g/day. In malnourished patients (weight below 50 kg), acute liver failure secondary to maximum dose oral paracetamol has been reported, and in this population, a dose reduction (max 2 g/day) is recommended [91].

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are more effective for persistent inflammatory pain than paracetamol [7, 59]. Despite good efficacy, NSAIDs must be used with caution in older people because of a high risk of potentially serious and life-threatening side effects [7]. Caution must be made in patients with low creatinine clearance, gastropathy, cardiovascular disease, or congestive heart failure. A study found that NSAIDs was implicated in up to a quarter (23.5%) of hospital admissions due to adverse drug reactions in older people [92]. NSAIDs may be considered as a treatment option when paracetamol or topical NSAID are ineffective or insufficient to treat osteoarthritis [93] and low back pain [94], considering the individual risk of side effects.

Opioider

Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain [59, 81, 83, 85]. In carefully selected and monitored patients, opioids can be used as part of a multimodal pain treatment also in patients with dementia. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient [81, 83, 85]. Due to reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose [81]. Thus, clinicians should

use additional caution and increased monitoring to minimize the risks of opioids prescribed for patients aged ≥65 years [81]. Age is a significant predictor in opioid-related harm with patients over 60 having a two to eightfold increased risk of respiratory depression, falls, and fracture [95], hospitalization and death [82, 96, 97]. For safety reasons, long-acting opioids should not be introduced before short-acting opioids.

Due to changes in gastrointestinal motility, elderly have an increased risk of suffering constipation when treated with an opioid and a laxative should be co-prescribed. Special caution should be made in patients with reduced renal function in whom treatment with tramadol, morphine, oxycodone, and fentanyl as these opioids are cleared by the kidneys, and there is a risk of reduced clearance of the drugs and increased susceptibility to accumulation of opioids and side effect. Buprenorphine is not cleared by the kidney and can be used in patients with reduced renal function.

There have been very few studies examining the effect and side effect of opioids in patients with dementia. At double-blinded trial of buprenorphine in people with advanced dementia found a high risk of adverse events, and the adverse symptoms that were described overlapped with common behavioral symptoms in dementia such as changes in personality, confusion, sedation or somnolence [98]. Opioids central side effects such as sedation, confusion, and dizziness pose a special concern in elderly with dementia as they, due to their brain diseases, are more susceptible to the central side effects. Furthermore, a considerable proportion of elderly with dementia receives another centrally acting drug such as a benzodiazepine or an antipsychotic drug [99, 100]. Sedative drugs such as antipsychotics, benzodiazepines, anxiolytics, hypnotics, antihistamines, tricyclic antidepressant all increase the risk of sedation and dizziness, and one should be especially cautious when initiating opioid treatment in a patient receiving either of these drugs. Recently, the US Federal Drug Administration issued their strongest warning against combining opioids and benzodiazepines due to the risk of serious adverse events and death [101]. Elderly with dementia are more susceptible to central side effects related to opioids and can experience a cognitive decline and loss of function when treated with an opioid. A recently published European Academy of Neurology guideline on medical management issues in dementia state that it is good clinical practice to consider discontinuation of opioids in patients for whom there are no complaints of pain and no clear indication, where mild analgesics have not been tried and in patients in whom there is suspicion of side effects, such as rapid cognitive decline, sedation, falls, respiratory problems, constipation, nausea, or reduced appetite [89].

Use of Analgesics in Elderly with Dementia

A common belief has been that elderly with dementia were being undertreated for pain due to a number of older studies showing that they were less likely to receive analgesics compared to cognitively intact elderly [16, 21, 102, 103]. However, over the past 15–20 year there have been increased prescribing of analgesics in elderly with dementia internationally [104–106]. Several more recent cohorts have shown

that elderly with dementia are prescribed analgesics more often than cognitively intact elderly [17, 107]. The largest study to date examining the use of opioids in elderly with and without dementia in the entire elderly Danish population found that among home-living elderly 27.5% of elderly with dementia prescribed an opioid and 16.9% of those without dementia. Among nursing home resident, use of opioids were higher and 37.8% of nursing home residents diagnosed with dementia and 43% of elderly not diagnosed with dementia received an opioid [107]. Elderly with dementia received longer use than elderly without dementia. Transdermal formulations were used by 2% of home-living without dementia, 11% of home-living elderly, and 19% of nursing home resident with and without dementia [107]. Furthermore, significant geographical variation in the use of opioids among elderly with dementia has been demonstrated [108], which was not explained by differences in age, sex, and comorbidity, suggesting different approaches towards either pain assessment and/or pain treatment in primary care.

Several factors may have influenced increases in opioid prescriptions. Clinicians are more cautious about NSAIDS and may prescribe opioids as an alternative. A Finnish study saw a reduction in NSAID use in nursing home facilities from 13.0% in 2003 to 2.6% in 2011 [109] as did a Norwegian study (6.8% in 2000 to 3.2% in 2011), alongside increases in opioids and acetaminophen [106]. Concerns have been expressed that opioids are used for their sedative effect, not just pain [104, 107, 109], especially since the increase in opioids has occurred concurrently with a decrease in the use of antipsychotics [104].

Dilemmas in Treating Pain in Dementia

Treating pain in the elderly with dementia is complex and challenging. The first challenge relates to identifying whether the patient is in pain. In patients with severe communication difficulties, pain assessment relies on observation. It can be difficult to judge whether a behavior is due to pain or not. The problems relating to assessment make it ethically challenging to start a treatment with potentially severe side effects if the indication for treatment is doubtful and the patient is unable to consent to treatment. The assessment of pain also poses a problem in relation to monitoring the effect and side effects of medication.

A second challenge relates to treatment. It is very much a balancing act between treating pain sufficiently and avoiding loss of function due to sedation and cognitive side effect, and in some cases, both will not be obtainable. Furthermore, there has been very limited research examining the effect and side effects of analgesics in the elderly with dementia.

Conclusion

Elderly with dementia report pain less frequently than cognitively intact elderly, but there is no evidence that they experience less pain. Assessment of pain gets increasingly difficult with an increasing degree of cognitive impairment.

Self-reporting of pain is the standard gold method for identifying pain in those with mild to moderate cognitive impairment. In the older person with severe cognitive impairment, observational assessment of behavior becomes essential for assessing the presence of pain and should follow a systematic approach to investigate the reason for the change in behavior. Treatment of pain follow the same guidelines as for elderly without dementia, but special caution should be made as elderly with dementia are more sensitive to the adverse effects associated with opioids.

Case 1

Mrs. P is an 80-year-old woman who was diagnosed with Alzheimer's disease 4 years ago and lives at a nursing home. She is a widow and moved to the nursing home 6 month prior. She suffers from osteoporosis, hypertension, and cataract, but is otherwise in good health. She suffers from moderate dementia, is apathic, and spends most of the time resting in an armchair.

She has been to a family birthday for 3 hours during the day. In the evening, she gets agitated and irritable. She paces around and does not sleep during the night. She is unable to express what is going on, but her behavior is very unusual. The staff initially thinks she has been overstimulated due to the family event. The following day she is still agitated and unable to find rest. The staff calls her primary care physician, and an examination of her urine is made, which shows traces of blood. On suspicion of a urinary tract infection, she is started on antibiotics. Over the next days she continues to be agitated. After 2 days she starts vomiting and develops a fever. She is admitted to the Hospital. On clinical examination, she is found to have a fever (38.9 °C), low blood pressure (98/60), is sweating and vomiting, and is restless. When her abdomen is examined, she is clearly tender in the right flank, which she expresses by frowning her face and saying "av." An X-ray shows obstruction of the right ureter, and she is diagnosed with kidney stones and acute pyelonephritis. She is treated with extracorporeal shock-wave lithotripsy to remove the kidney stone and iv antibiotics and iv fluids due to sepsis. After removal of the kidney stone, the agitation subsides.

Note: When elderly with dementia develop new behavioral symptoms, a physical cause should always be suspected, and a thorough examination of the patient should be made. In this case, the patient was not able to express what is going on but express pain by developing agitation, restlessness, and disrupted sleep. When a thorough examination was made, she is able to say that it hurts but also expresses pain by facial expressions, when the doctor examines her right flank.

Case 2

Mrs. E is an 85-year-old woman, who was diagnosed with Alzheimer's disease 5 years ago. She suffered a stroke 1 year ago, which left her with a right-sided hemiparesis and aphasia. She is unable to walk and spends the day either in a well-chair

or in bed. She also suffers from osteoporosis and is treated with paracetamol 1 g × 4 daily due to pain. Due to spasticity in the right side she receives baclofen 10 mg × 3 daily but has been unable to tolerate higher doses due to sedation. The family physician visits the nursing home and notices that Mrs. E. is screaming. The staff informs him that over the past 2–3 weeks, she has been screaming a lot and been very aggressive and uncooperative during care. The staff think she may be in pain. A systematic evaluation of the patient is made. Due to her not being able to communicate, an observational scale is used (in this case PAINAD), where she scores 4/10 (2 points on vocalization due to "repeated troubling calling out," 1 point on body language due to being tense and 1 point on consolability due to intermittently being distracted by calming talking to her). She is transferred to her bed, and a new assessment is made in order to investigate if this is related to movement. The score increases to 6 due to facial grimacing. A thorough clinical examination is made, which shows a small sacral pressure ulcer. There was also tenderness of the vertebrae at L3 and L4. When moving her right-sided extremities, there was the stiffness of the right arm and upcoming contracture. During the examination mrs E. reacted with restlessness, resistance, and vocalization. It was suspected that pain was the cause of the vocalization and resistance to care as she was unable to express that she was in pain.

Mrs. E. had several reasons for experiencing pain, i.e., a new pressure ulcer, chronic pain due to osteoporosis and developing a contracture. Several non-pharmacological measures were instituted, such as physiotherapy for the contracture, an air madras in her bed, and special pillow in her wheelchair. Furthermore, the staff was made aware that the care and transfer caused pain and found alternate ways. An analgesic trial with morphine 10 mg × 3 daily was instituted as the patient already received paracetamol, and a follow-up 4 days later was arranged. When the physician consulted her 4 days later, he found that she was calmer but also sedated by morphine and spend most of the day sleeping. The dose of morphine was reduced to 5 mg half an hour before care twice daily, which she was able to tolerate without being sedated. A follow-up 1 week later was arranged. At the next consultation, the sacral pressure wound had almost heeled. The patient reacted with less resistance to care, but still had some calling out and had decreased to a 3/10 on PAINAD on transfer. A follow-up 3 weeks later was arranged, where the pressure ulcer was completely healed, and the contracture in the right arm improved. It was possible to discontinue the morphine. Mrs. E. still had episodes of calling out but did not resist care.

Note: in this case, the patient is unable to communicate, and an observational assessment of pain is made. The patient is found to have multiple potential causes of pain aside from potential chronic pain due to osteoporosis. She is also treated with baclofen due to spasticity, and due to the combined sedative load, she is only able to tolerate a small dose of morphine. When starting an analgesic, it is always important to arrange for a follow-up, where effect and side effects are evaluated, and a plan for discontinuation is made. It is also important to be aware of other centrally acting medication, such as antipsychotics, benzodiazepines, hypnotics, etc., which can increase sedation and make side effects unwarranted due to potential loss of function.

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