Assessment and treatment of pain in people with dementia

Anne Corbett, Bettina Husebo, Marzia Malcangio, Amelia Staniland, Jiska Cohen-Mansfield, Dag Aarsland and Clive Ballard

Abstract | Many elderly people experience pain and regularly take analgesic medication. Pain is also frequent in people with dementia, particularly those with severe disease. As no robust clinical guidelines are available for the treatment of pain in the context of dementia, the risk of inadequate treatment in individuals with this condition is high. Furthermore, our understanding of the aetiology of pain and the potential role of dementia-associated neuropathology in pain is limited. These issues are important in the clinical management of individuals with dementia, as untreated pain is a major contributor to reduced quality of life and disability, and can lead to increased behavioural and psychological symptoms. Assessment scales to identify pain in people with dementia have been highlighted in recent studies, but there is little evidence for consistency between these tools. Numerous studies have evaluated various approaches for the treatment of pain, including stepped-care protocols and/or administration of paracetamol and opioid medications. In this Review, we summarize the best-available evidence regarding the aetiology, assessment and treatment of pain in people with dementia. Further validation of assessment tools and large-scale trials of treatment approaches in people with dementia are needed to improve clinical guidance for the treatment of pain in these individuals.

Corbett, A. *et al. Nat. Rev. Neurol.* **8**, 264–274 (2012); published online 10 April 2012; doi:10.1038/nrneurol.2012.53

Introduction

More than 30 million people worldwide have dementia, and this figure is expected to increase to 100 million by the year 2050.[1] Dementia is a devastating disease that is characterized by progressive cognitive and functional decline, often with neuropsychiatric symptoms. The disease can lead to loss of independence, incapacity and, eventually, death. Dementia is caused by a diverse group of diseases, of which the most common is Alzheimer disease (AD)—a disorder that is characterized by accumulation of the proteins amyloid-β and tau in the brain, which form amyloid plaques and neurofibrillary tangles, respectively. The disease causes great distress to the individual, as well as to those caring for them, and imposes a huge financial cost on society. The clinical challenge of treating individuals with dementia is often exacerbated by the communication difficulties that are experienced by the majority of people with the disease, particularly in the later stages when language, cognition and self-care abilities are severely impaired.[2] Evidence suggests that the inability to communicate thoughts and feelings leads to substantial unmet needs in individuals with dementia. One such unmet need is the identification and treatment of pain.

Untreated pain is not only distressing for the person, but also impairs social interactions, quality of life and appetite, and results in sleep disturbances.[3–5] Pain can often be a contributory cause to behavioural and psychological symptoms of dementia, such as aggression, agitation and psychosis (hallucinations and delusions),[6] and to mood disorders such as depression. Although the complications of pain in individuals with dementia are well-documented, clear guidance on the best approaches for the measurement and treatment of pain in these individuals is lacking. Despite our understanding of the altered biological processing of pain in individuals with dementia, the optimal clinical treatments for different types of pain remain unclear. Several helpful reviews on specific aspects of pain in dementia have been published over the past decade, but none has comprehensively addressed the full spectrum of the complications associated with pain in the context of dementia. A number of studies to investigate the assessment and treatment of pain in people with dementia have also been performed over the past 2 years.

In this Review, we aim to provide a comprehensive overview of current evidence regarding pain in dementia to guide the evidence-based assessment and treatment of pain in individuals with this disease. Furthermore, we focus on the key gaps in our current knowledge of pain in dementia, and highlight the priorities for further biological and clinical research in this field.

Alzheimer's Society, 58 St Katharine's Way, London E1W 1LB, UK (**A. Corbett**). University of Bergen, Department of Public Health and Primary Health Care, Kalfarveien 31, N-5018 Bergen, Norway (**B. Husebo**). Wolfson Centre for Age-Related Diseases, Wolfson Wing, Hodgkin Building, King's College London, Guy's Campus, London SE1 1UL, UK (**M. Malcangio, C. Ballard**). Sackler Faculty of Medicine, School of Public Health, Tel Aviv University, Ramat Aviv, PO Box 39040, Tel Aviv, Israel (**J. Cohen-Mansfield**). University Hospital Stavanger, Centre for Clinical Neuroscience Research, PO Box 8100, 4068 Stavangar, Norway (**D. Aarsland**)

Correspondence to: C. Ballard clive.ballard@kcl.ac.uk

Competing interests
A. Corbett declares associations with the following companies: Acadia, Lundbeck, Novartis. C. Ballard declares associations with the following companies: Acadia, Bristol-Myers Squibb, Esai, Janssen, Lundbeck, Novartis, Shire. D. Aarsland declares associations with the following companies: DiaGenic, GE Healthcare, GlaxoSmithKline, Lundbeck, Merck Serono, Novartis. The other authors declare no competing interests.

Prevalence of pain

Chronic musculoskeletal pain affects over 100 million people in Europe, and is by far the most common factor that limits the activities of the ageing population. Persistent pain is associated with reduced mobility, as well as disability, muscle weakness and falls, and can affect mental health and quality of life.[7] Prevalence of pain among older adults (over 60 years old) is difficult to quantify. In one study, 19% of community-dwelling adults over 80 years of age reported that they were experiencing pain,[8] and a further estimate indicated that over one-third of community-dwelling older adults frequently experienced pain.[9] Analgesic use in people over 80 years of age was high: 50% were reported to be regularly taking analgesic medications.

Although few studies that examine the prevalence of pain in people with dementia exist, there is good agreement across both large and small studies that about 50% of people with dementia regularly experience pain.[10–12] This estimate has recently been confirmed in a large community study in Canada that involved 5,703 elderly outpatients, 456 of whom had dementia. Non-cancer-related pain was reported in 52.1% of people with dementia, which is comparable to 56.2% of people without cognitive impairment.[13] In a further large study of patients at a geriatric clinic, 52% of people with dementia were found to be in pain.[14]

Severity of pain is directly correlated with the severity of both dementia and functional impairment. Accordingly, pain is reported in a higher proportion of people with dementia who require care home living than in those who do not require 24-h assistance. At least two-thirds of older people living in nursing homes have dementia, and up to 80% of nursing home patients are in acute or chronic pain. The majority of these individuals experience persistent pain (lasting 3–6 months or longer)[15] that is often, but not exclusively, related to the musculoskeletal system.[16] People with dementia who live in care homes are also particularly susceptible to genitourinary infection and its associated pain. Furthermore, for patients in the severe stages of dementia, pressure ulcers in the skin are a major cause of pain. Additional conditions that cause pain in people with dementia (as well as in the general population) include gastrointestinal complications such as peptic ulcers, intestinal obstruction and peritonitis, cardiac issues such as ischemia and myocardial infarct, and skin problems other than ulcers.[17,18]

Biology of pain in dementia

Owing to the neuropathological and biochemical changes associated with dementia, a common perception is that people with this condition may not feel pain to the same degree as older adults without cognitive impairment. How the biological pathways of pain are affected in the different types of dementia is not well-understood, but determining whether pain is truly less common or simply underdiagnosed in individuals with dementia compared with those without cognitive impairment is critical. This understanding is also important for the development of appropriate treatments for pain in people with dementia.

Key points

- Pain is common in people with dementia, and many of these individuals are prescribed analgesic medication
- Clinical guidance and validated assessment tools to manage and detect pain in patients with dementia are limited, which may lead to inappropriate treatment and/or underdiagnosis of pain in these individuals
- Evidence to support the hypothesis that dementia-associated neuropathology results in less-frequent or less-severe pain in patients with Alzheimer disease is not robust
- Practical and simple methods for the assessment of pain in people with dementia are required for use in the clinical setting
- Evidence is available to support the use of analgesic medication, particularly paracetamol, to address pain in people with dementia
- Future trials to address pain in patients with dementia should focus on the value of nonpharmacological treatments, stepped-care approaches, and NSAIDs

Pain is described as an unpleasant sensory and emotional experience in response to an actual or potential threat to the integrity of the body and, as such, is a protective mechanism.[19] Loss of this protective mechanism, as observed in conditions such as leprosy, is associated with considerable physical consequences and interferes with quality of life. Loss of pain perception in people with dementia could have similar implications.

Acute pain perception, such as exposure to a hot surface, involves specialized sensory neurons—C-fibres and Aδ-fibres—that convey the stimulus to dorsal horn neurons in the spinal cord. The signal then ascends via the thalamus, amygdala and hypothalamus to the somatosensory cortex where the intensity and type of pain is perceived. A parallel pathway ascends from the dorsal horn to the limbic system where the emotional component is registered. The withdrawal response is then mediated by spinal reflexes.[19] In people with AD, the emotional component of acute pain is reported to be significantly reduced.[20] Notably, one study reported that patients with AD had an elevated pain tolerance (associated with the emotional–affective pain component): the patients tolerated ischemic pain in the arm for longer than did age-matched non-AD controls.[21] Other findings suggest that the threshold for detecting pain may be lower in individuals with AD than in healthy individuals.[22]

Chronic pain is profoundly different from acute pain, in that it occurs as a result of plastic changes within the pain pathways.[23] This form of pain is defined as a debilitating condition lasting longer than 3 months, and is characterized by pain that is out of proportion to the inciting injury. Chronic neuropathic and musculoskeletal pain, such as that associated with diabetic neuropathy or osteoarthritis, can be objectively identified in patients by their increased sensitivity to painful stimuli (hyperalgesia) and painful response to non-noxious stimuli (allodynia). Reliable information about hyperalgesia and allodynia in people with dementia is limited, as neurological examinations, including sensitivity to temperature, pain and tactile stimuli, are not part of a standard clinical assessment of these individuals. However, allodynia may be a plausible explanation for

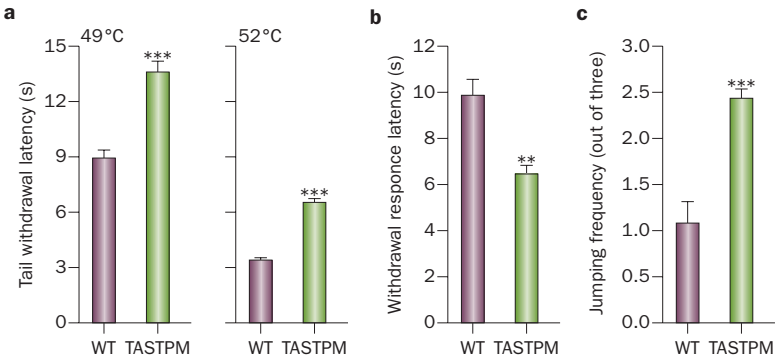

Figure 1 | Response to acute pain behaviour in mouse models of AD. Naive TASTPM mice were exposed to acute noxious stimuli and compared with WT controls. **a** | Compared with WT mice, TASTPM mice had a longer latency to tail withdrawal following immersion in water held at either 49 °C or 52 °C, demonstrating a relative insensitivity to noxious thermal stimuli in AD-like mice. **b** | Latency of tail withdrawal response in the hot-plate test was reduced in TASTPM mice compared with control mice. **c** | TASTPM mice had an increased frequency of jumping from the hot plate compared with control mice, demonstrating a reduced quality of withdrawal response in the AD-like animals. Data are shown as mean ± SEM. $n = 15–23$ mice per genotype, $^{**}P<0.01$, $^{***}P<0.001$. Abbreviations: AD, Alzheimer disease; WT, wild-type.

abnormal behaviours of individuals with dementia, such as the aggressive reaction to intimate personal care.[24] Some rationale exists for the theory that the perception of chronic pain is reduced in patients with AD as a consequence of the characteristic neuropathology of the disease, which may damage or block pain pathways.[25] Reduced pain perception owing to dementia-associated neuropathology could contribute to the delayed diagnosis of chronic conditions such as osteoarthritis, for which pain is an early and ongoing symptom.[26,27]

One proposal is that reduced reporting of pain in people with AD is a consequence of neuropathology that negatively affects the amygdala and hypothalamus[24] while sparing the somatosensory cortex.[24,28] However, this interpretation fails to take into account the fact that AD pathology also occurs in other regions of the brain. For example, amyloid-β deposition has been observed in key areas that are responsible for pain processing, including the thalamic intralaminar nuclei.[24] Furthermore, the presence of neurofibrillary tangles in the dorsal horn of the spinal cord has been reported in some AD patients,[29] and preclinical studies reported some degree of axonal pathology in the spinal cord of transgenic mouse models of the disease.[30] Evidence to support altered processing of certain types of pain in patients with dementia also exists: functional connectivity between the dorsolateral prefrontal cortex and the anterior midcingulate cortex, periaqueductal grey matter, thalamus, hypothalamus and several motor areas was enhanced in patients with AD compared with controls.[31]

Pain-response behaviours to mechanical and thermal stimuli have been assessed in transgenic rodent models of AD (TASTPM mice) compared with age-matched control animals (C. Ballard, unpublished work). Transgenic mice were similarto control mice with regard to paw withdrawal response to mechanical stimuli, but exhibited delayed withdrawal in response to thermal stimulation (Figure 1). Transgenic animals were also significantly slower to react to tail immersion in heated water than were controls, indicating insensitivity to acute thermal pain stimuli in animals that expressed a mutant amyloid precursor protein. Interestingly, AD-like mice also exhibited an abnormal behavioural response to pain in a 'hot-plate test', with a higher likelihood of jumping to escape from the stimulus and a lower likelihood of lifting and licking their hindpaws compared with control mice (Figure 1).

Overall, the preliminary evidence indicates that people with AD and transgenic animals with AD-like pathology have subtle alterations in both cortical and emotional perception of pain and in processing and behavioural response to pain. Some aspects of chronic pain are suggested to be less frequent in individuals with AD than in those without cognitive impairment; however, as current knowledge on pain processing in dementia is limited, one cannot assume that pain is significantly less frequent in people with AD than in older adults without the disease. Indeed, the available evidence suggests that patients with AD may have subtle alterations in pain perception and processing relating to a specific type of pain. Key questions that remain to be addressed include whether an improved understanding of the effects of AD on pain perception will help to inform better clinical management, and whether this effect depends on the type of pain and the underlying condition that is responsible for the pain.

Prescription of analgesic medication

Traditionally, medications with analgesic effects are classified into three groups: peripheral analgesics (such as paracetamol), NSAIDs, and opioid agents. Additional medications that may be administered to patients experiencing pain include antidepressants, anticonvulsants, hypnotics, anxiolytics, antipsychotics and steroids. Even when a person is recognized as being in pain, the prescription of analgesic medication often falls short of best-practice recommendations—a worldwide problem that has been documented in studies from the Netherlands, Belgium, UK, Norway, Sweden, USA and China.[32–34]

Results from the literature indicate that analgesic use is higher among people with dementia than in older adults without dementia; however, the majority of these studies were undertaken in Scandinavia so may not be indicative of treatment elsewhere. In one Swedish study, published in 2011, researchers reported that despite less-frequent self-reporting of pain in patients with AD, 46% of people with dementia received analgesic medications compared with only 25% of their cognitively healthy counterparts.[35] Analysis of analgesic use in older adults in Sweden and Finland showed that the use of paracetamol, antipsychotics and antidepressants was more common in people with dementia than in those without dementia.[36] However, no difference was found between the two groups in the use of opioid analgesics, anticonvulsants or hypnotic medications. Baseline data from a randomized controlled trial (RCT) performed in Norway indicated

that 37% of people with dementia in care homes regularly received oral analgesics, and a further fraction of individuals with dementia received prescribed topical analgesics.[37] Another study suggested that overall use of opioids was lower in people with AD than those without AD,[38] but the authors noted increased use of the transdermal preparation of the opioid fentanyl—a drug that is associated with morbidity and death in previously opioid-naive patients—in the AD group.[39,40] In addition, compared with elderly patients without dementia, people with dementia were more likely to be given as-needed medication for pain than daily analgesic medication.[41,42]

Timely and effective assessment and treatment of pain is critical to improve quality of life of people with dementia. Overall, the results from published studies do not suggest that analgesic medications are systematically underprescribed to people with dementia. A key consideration will be to optimize the use of different pharmacological approaches while balancing the imperative of achieving effective analgesia with the adverse effects and harm that are associated with polypharmacy.[43,44] In addition, the high frequency of prescription of analgesics does not necessarily mean that appropriate treatment is being given to the right individual at the right time. Among individuals with dementia, targeting of the appropriate medication to each patient will depend on the timely identification and assessment of pain. Findings from three studies support the value of educational training for nursing and care staff in improving pain assessment and analgesic-prescribing practice.[45–47]

Pain assessment in dementia

Valid and accurate measurement of pain is a major prerequisite for a successful trial of pain treatment and to assess the potential adverse effects of analgesic medications. Newly developed instruments to measure pain are often derivatives of existing rating tools that encompass different aspects of pain behaviour and intensity; location and duration of pain; observation of pain in rest or during movement; and self-report of pain where possible. Accurate assessment of pain, therefore, depends on the patient's memory, expectation of improvement, and capacity for self-report.[48,49] Patients with moderate dementia seem able to use some of the available self-reporting instruments;[50] however, owing to various factors (including communication difficulties), underdiagnosis of pain in older adults with dementia, especially in those in the advanced stages of dementia, is a particular risk.[51,52]

Pain is often chronic and unrecognized by the person experiencing it, and may be only one of many simultaneously discomforting conditions. In recognition of these complicating factors, the American Geriatric Society (AGS) convened a series of three complementary panels of physicians to focus on persistent pain in older adults, the pharmacological management of persistent pain, and the management of chronic pain. The reports from the panels highlighted the variability and complexity of pain diagnosis, physical disabilities and analgesic use in people with dementia,[41,53,54] and recommended a comprehensive, disease-specific assessment of each patient's typical pain behaviour using a validated pain assessment tool as a prerequisite to determine the appropriate treatment for each individual.

Over the past 30 years, more than 35 pain assessment instruments for older people with dementia have been developed, tested, and reviewed in the literature.[55–59] Most of these instruments were developed on the basis of the assumption that a patient communicates acute or chronic pain through changes in facial expression, vocalization and body movements.[54] One study suggested that the primary function of pain behaviour is to enlist the aid of others.[60] The Facial Action Coding System (FACS) has long been used to document and analyse pain behaviour in adults in the form of facial actions recorded by use of video recording and photography.[60–62] FACS analysis showed that facial responses to noxious stimulation were significantly increased in patients with dementia compared with healthy controls, and that the increase in facial responses directly correlated with increased intensity of pain.[63] The assessment of facial expressions associated with pain, therefore, has the potential to serve as a valid alternative to self-report rating scales in patients with dementia.

One of the first standardized rating instruments for nurse observation of patient pain behaviour was the Observational Pain Behaviour Assessment Instrument (OPBAI), which encompasses 17 items on a seven-point scale.[64] An early validation study emphasized that use of the scale required an observer to judge whether the behaviour was related to pain or was a response to factors other than pain. Furthermore, discrepancies between observer and patient ratings of pain were found to be greater when rating chronic pain than when rating acute pain. Since the development of the FACS in 1978 and the OPBAI in 1983, clinicians and researchers have made substantial efforts towards improving detection of pain in people with dementia. Currently, there are four types of pain assessment for use in people with dementia at all stages of the condition: self-report, observational, caregiver rating, and interactive (Box 1, Supplementary Table 1 online). Of the 35 assessment tools in existence, only those with the best-reported psychometric properties and clinical utility are discussed below.

Self-report assessment

Self-report is the most appropriate assessment tool for the early stages of dementia when pain can still be recognized and verbalized by the patient.[65] Self-assessment relies on rating of pain in the present or retrospectively, such as with the eight-point Present Pain Intensity scale, which shows reasonable reliability and validity to detect pain in people with dementia (Supplementary Table 1 online).[59] Several other scales have been examined in people with dementia, including verbal rating scales, numerical rating scales and faces scales;[50] however, further work is needed to formally validate the utility of these instruments. The self-report approach is less reliable, and often less applicable, for patients in the advanced stages of dementia.[66]

Box 1 | Examples of tools to assess pain in patients with dementia

Self-report
- Present Pain Intensity (PPI) scale, report of pain experienced now versus last week[59,71,94]

Caregiver or informant rating
- Pain Assessment for the Dementing Elderly (PADE) and global staff rating[70]
- Pain Assessment Instrument in Noncommunicative Elderly persons (PAINE)[69]
- Abbey Pain Scale[95]

Observational rating
- Discomfort Scale for Dementia of Alzheimer's Type (DS-DAT)[96]
- Checklist of Nonverbal Pain Indicators (CNPI)[97]
- Pain Assessment in Advanced Dementia (PAINAD)[98]
- Elderly Caring Assessment 2 (EPCA-2)[99]
- DOLOPLUS-2[100,101]
- Non-communicative Patient's Pain Assessment Instrument (NOPPAIN)[102]
- Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale[72,73]
- Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC)[103]
- Dutch-translated Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC-D)[12]

Interactive rating scale
- Assessment of Discomfort in Dementia (ADD) Protocol[85]

Caregiver rating assessment

Tools to enable assessment of pain by the caregiver have also been applied and used in research to evaluate approaches to management and treatment of pain in people with dementia. Informant-based ratings are significantly more accurate if the caregiver is in at least daily contact with the person with dementia.[67] Caregiver rating scales include the 24-item Pain Assessment for the Dementing Elderly, the 22-item Pain Assessment in Non-Communicative Elderly Scale, and the six-item Abbey Pain Scale (Box 1). The utility of these tools relies on caregiver identification of pain-related behaviours such as facial expressions, verbalizations, body movements, and changes in activity patterns or routines.[55,67–70] Initial validity testing in small patient sample groups showed promising outcomes (Supplementary Table 1 online), although testing in large patient samples is required. The time required for staff training in the use of caregiver-based pain-rating tools is an important additional consideration that should be addressed in future studies.

Observational assessment

Observational tools to assess pain include the Discomfort Scale for Dementia of Alzheimer Type (DS-DAT), the Checklist of Nonverbal Pain Indicators (CNPI), the Pain Assessment in Advanced Dementia, the DOLOPLUS-2, the Pain Assessment Checklist for Seniors with Limited Ability to Communicate, the Non-Communicative Patient's Pain Assessment Instrument, and the Elderly Caring Assessment 2 (EPCA-2). Many of these tools were developed on the basis of recommendations from the AGS panels and focus on observation of patient behaviour, including their ability to perform specific daily tasks and activities. Of these observational pain assessment tools, some show good reliability, whereas others require further evaluation (Supplementary Table 1 online). Although some observational instruments demonstrated potential for detecting pain in nonverbal older adults with dementia, none showed sufficient practical utility as a tool to inform the physician as to the optimal timing of pain treatment.[71] Owing to the intensive observation required with a number of the instruments, such as with the DS-DAT and EPCA-2 scales, these tools may hold more potential in research than as routine tests in the clinical setting.

The Mobilization-Observation-Behaviour-Intensity-Dementia Pain Scale (MOBID-2) was developed in 2007 and seems to be more robust than previous observation instruments. Ratings on this scale are made on the basis of pain behaviour following the performance of a series of prescribed physical movements. This instrument adds new perspectives relating to the location of pain and the interpretation of pain intensity from observed pain behaviours. Studies indicate high to excellent aspects of reliability and validity of this assessment scale, including feasibility in clinical practice.[72–75]

Interactive assessment

In response to the various methodological limitations, an interactive method entitled the Assessment of Discomfort in Dementia (ADD) protocol was developed to identify, and thus enable the management of, challenging behaviours.[76,77] In addition to identifying pain, the ADD is a nurse-administered intervention that includes a physical and affective needs assessment, a review of the patient's history, and the administration of analgesic medication.[76] The ADD intervention is based on the assumption that psychiatric behaviours associated with dementia are manifestations of unmet needs.[78] The value of this approach as a clinical intervention protocol for the assessment and management of unmet needs in people with late-stage dementia has been demonstrated.[79]

Recommendations for pain assessment

A number of promising pain assessment tools are available, but the majority of these require validation in people with dementia. Nonetheless, evidence is emerging that several assessment approaches, including MOBID-2, enable the effective identification of pain and pain-related behaviour in this patient group. Furthermore, these instruments are sensitive for detecting changes in pain intensity during treatment studies. One should note, however, that agreement between different types of assessment instrument is limited, and some of the tools are yet to be validated in English-speaking populations.[57] Evidence to support the value of cerebrospinal fluid biomarkers for pain is growing; these markers may enable better identification of pain with improved accuracy of diagnosis, particularly for pain that arises as a result of inflammation.[80] Biomarkers such as neuropeptides, which can be linked to nociceptive activity, may be a promising approach to identify patients who are experiencing pain, although these biomarkers would need to be validated using pain assessment tools.[81] The potential role of biomarkers for detecting pain is an important agenda for future research.

In clinical practice, identification and monitoring of pain is the most critical concern; thus, the use of at least two different assessment approaches (for example MOBID-2 and the assessment component of the ADD protocol) is suggested. Treatment for pain is suggested if assessment using either of the two instruments indicates that the patient is in substantial pain. To maintain consistency, this two-assessment approach could then be used to monitor the patient for any benefits following treatment. In research settings, accurate measurement of pain (rather than identification of pain) may be of greater concern than in the clinic, as these measurements reflect the integrity of outcomes. In this setting, therefore, pain should be identified by use of at least two independent instruments to ensure a robust diagnosis of pain.

Pharmacological treatment of pain

Nine fully randomized prospective treatment studies with a comparator group, or open studies with more than 10 participants, have evaluated the efficacy of analgesia in people with dementia (Supplementary Table 2 online). These studies used standardized outcome measurements and follow-up procedures to assess outcomes following each treatment regimen, specifically in patients with cognitive impairment.

Parallel-group randomized controlled trials

Kovach *et al.*[79] reported results from a 4-week double-blind RCT involving 114 participants with moderate to severe dementia (Mini-Mental State Examination [MMSE] score <26, specific types of dementia not reported) and behavioural symptoms, recruited from 14 nursing homes. Patients were randomly assigned to either a nurse-led stepped-treatment programme (Serial Trial Intervention [STI]) or a control programme of usual care. Following assessment of physical and affective factors, patients in the STI group initially received nonpharmacological 'comfort' treatments based on principles of person-centred care. If symptoms did not improve by at least 50%, the patient received as-required prescription of an analgesic. If there was still less than 50% improvement in symptoms, the patient then attended a specialist consultation, where an antipsychotic medication might be prescribed. Ratings according to the DS-DAT were made on the basis of vocalization, breathing, facial expressions and body movement over a period of 5 min, as observed by research assistants who were blinded to treatment. Compared with patients in the control treatment arm, the intervention group had significantly reduced levels of discomfort (DS-DAT, $F = 9.64$, $P < 0.01$). Patients in the STI group also had improved behavioural symptoms on the nurse-administered Visual Analogue Scale ($F = 0.70$, $P = 0.50$), but not on the Behavioral Pathology in Alzheimer Disease Rating Scale, when compared with controls. The treatment group received more specialist consultation sessions and analgesic prescriptions than did the control group (46% versus 3%).

In a small placebo-controlled, double-blinded crossover study, Manfredi[82] and colleagues evaluated treatment with opioid analgesics in 25 people with severe dementia (MMSE score <21) and agitation who lived in one residential home. The participants had all previously received antipsychotic medications with unsatisfactory outcomes with regard to agitation. Each patient entered a 4-week placebo phase followed by a 4-week treatment phase to avoid confounding effects from opioid withdrawal. Notably, this approach precluded the possibility of a randomized order of treatments. Medication was administered as 10 mg of oral oxycodone twice a day, or 20 mg morphine once a day for participants who were unable to swallow pills. Analysis of agitation using the Cohen-Mansfield Agitation Inventory (CMAI) showed no significant difference between the placebo and treatment phases. Although participants showed a small improvement of 5 points on the CMAI during the placebo phase, only a further 1-point improvement was observed during the period of opioid treatment. The authors reported a statistically significant reduction in agitation at the end of the opioid treatment phase in a subgroup analysis of 13 patients over 85 years old, although there was a similar 5-point improvement on the CMAI score during the placebo phase in those under the age of 85 years. There was no difference in sedation or use of as-required antipsychotic medication between the two phases of the study.

Husebo and colleagues[37] performed a cluster RCT to evaluate a stepwise protocol for the treatment of pain in 352 people with moderate to severe dementia and significant behavioural symptoms. Patients in 60 clusters from 18 Norwegian nursing homes were randomly assigned to receive either usual treatment (control group) or an 8-week stepwise protocol of analgesic administration, with medication choice depending on prior treatment and assessment of pain. 111 participants (63%) received step-one treatment with paracetamol, with nine (5%) receiving an increased dose of an existing prescription. 2% of the patients received step-two treatment (oral morphine to a maximum of 20 mg/day), 18% received step-three treatment (buprenophine transdermal patch, maximum dose of 10 μg/day), and 4% received step-four medication (oral pregabalin, maximum dose 300 mg/day). For the intervention compared with control treatment, the findings revealed an overall statistically significant improvement in agitation (CMAI median scores 52.8 versus 46.9), aggression (CNPI scores 26.9 versus 21.0) and pain (MOBID-2 scores 3.5 versus 2.3). Furthermore, patients in the intervention group showed significant worsening of symptoms during the 4-week withdrawal phase compared with those who received usual care. There was no difference in cognition or ability to perform activities of daily living between patients in the two groups. Unfortunately, as the authors did not perform a subanalysis of people receiving the different levels of treatment, no conclusions can be drawn regarding the efficacy of each of the prescribed treatments.

Crossover randomized controlled trials

Treatment with paracetamol was assessed in a double-blind, placebo-controlled trial that included 25 people

with moderate to severe dementia from two nursing homes.[83] Participants were randomly assigned to a control group or to an intervention consisting of paracetamol (3 g/day) for 4 weeks and a 4-week placebo phase. The order of treatment was determined by randomization, with a 1-week wash-out period in between treatment arms. Function was assessed using the Functional Assessment Staging Tool, but no assessment of specific dementia diagnoses was made. The authors reported significant improvement in activities (measured using Dementia Care Mapping) in patients who received paracetamol compared with those in the placebo group: more patients participated in social interaction, media engagement, and work-like activities. However, paracetamol treatment was not associated with improvement in sleep or well-being. In addition, no improvement was identified in mobility or agitation (as rated using the CMAI) in patients receiving the treatment. As no measures of pain and discomfort were reported in this study, interpretation of these findings with regard to efficacy on reducing pain is difficult.

The efficacy of regularly scheduled analgesic treatment for discomfort in people with moderate to severe dementia was evaluated in a 4-week placebo-controlled crossover study involving 39 patients.[84] Participants with a painful condition were randomly assigned to receive either 650 mg/day paracetamol as needed and a placebo administered four times per day, or placebo as needed and 650 mg paracetamol four times per day, for 2 weeks. Participants on one protocol were switched to the other treatment arm after 2 weeks. Regular paracetamol did not confer any benefit with respect to discomfort, as measured using the DS-DAT. However, throughout the trial only seven patients received the as-needed medication: three received paracetamol during the placebo arm and four received placebo during the treatment arm. As the dosage of paracetamol used in this experiment was low, the medication might have been insufficient to address pain in older adults with dementia.

Observational or comparator studies

Cohen-Mansfield and colleagues performed an open-treatment trial to analyse the effectiveness of analgesia in 121 people with dementia living in nursing homes.[67] All participants who were considered to be in pain at baseline received a pain medication protocol involving an escalating dose of paracetamol with oxycodon or oxycontin that was given four times per day. The study included three comparator groups: people who were in pain at baseline and followed the treatment protocol, people who were in pain at baseline but whose caregivers choose not to follow the medication protocol, and people who were not in pain and so did not receive any medication.

Participants who received the medication protocol had a significant reduction in pain over the period of the study compared with the other two groups. All participants in the medication arm were considered to be pain-free by the end of the study, but this group had a high rate of dropout, as many carergivers chose not to follow the protocol because they did not wish to prescribe high doses of paracetamol or opiates to their patients. Individuals in this scenario were classed in a separate comparator group and given a final evaluation. At the end of the study, 17 patients were receiving 1,000 mg acetaminophen, 11 were on 650 mg acetaminophen, five were taking 1,000 mg acetaminophen with 2.5 mg oxycodone, and one patient each was receiving 1,000 mg acetaminophen with 5 mg oxycodone, 640 mg acetaminophen (liquid), or medication to treat cough. Interpretation of this study to determine which medication and protocol was superior for the treatment of pain is limited by a lack of focus on the specific treatments received.

The ADD protocol was evaluated in an exploratory study of 143 people with dementia who lived in nursing homes.[85] Participants who were identified as being in pain were treated with either a nonpharmacological approach or an analgesic. Use of the ADD protocol was triggered when basic-need interventions had failed and when behavioural symptoms were highlighted according to assessment using the Minimum Data Set. Step one of treatment was assessment using the ADD protocol. Step two was an analysis of records showing the patient's history of pain. Step three involved an assessment of person-centred care received by the patient, including environmental pressures, activities and/or stimulation that were experienced during usual care (including nonpharmacological interventions). Step four involved administration of a non-narcotic analgesic, usually paracetamol, and step five was administration of as-needed psychotropic medication, as determined by the medical professional. In this study, only 37% of people who received nonpharmacological interventions showed improvement in discomfort rating compared with 83.5% of people who received analgesic medication.

Stein and colleagues[45] performed a 3-month RCT to evaluate the effectiveness of an educational training package for care staff to improve administration of analgesic medication and optimize the use of NSAIDs. The study involved 147 older nursing home residents. Care staff were given training in the benefits and adverse effects of NSAIDs, and provided with support to consider alternative medications. Education of staff using the training package resulted in a significant reduction in the use of NSAIDs: the time of NSAID use was reduced from 7.0 days to 1.9 days in patients treated by care staff who received training compared, with a reduction from 7.0 days to 6.2 days in the usual-care group. Notably, the reduced use of NSAIDs was not associated with worsening of pain.

The largest trial of stepped analgesia in people with agitation in the context of dementia was a cluster RCT in which the researchers reported statistically significant reductions in agitation and pain following active analgesic treatment.[37] Although the majority of participants received only paracetamol, there was no separate analysis of people receiving different analgesic regimes, and the cluster design of this trial may have created the potential for a Hawthorne effect—the tendency to perform better when participating in a trial—in the active treatment

arm. Results from several open-label or crossover studies that did not require the presence of behavioural or psychological symptoms as an entry criterion have suggested that stepped analgesic treatment decreases pain or discomfort in people with dementia who experience pain at baseline.[67] However, these results must be interpreted cautiously due to the limitations in the design and size of these studies.

Small underpowered trials

Other small, underpowered crossover trials have investigated paracetamol treatment in patients with dementia, but the findings are difficult to interpret owing to the absence of direct measures of pain or discomfort, or the use of very low doses of paracetamol. One study had the specific aim of optimizing NSAID use in patients with dementia; however, in the absence of any studies to evaluate the potential benefits of NSAIDS as analgesics in people with dementia, interpretation of the findings from this study is difficult. In several open-label trials and cluster trials, opioid treatment was administered as part of stepped analgesia, but the outcomes associated with receipt of this treatment alone were not reported. The only trial that directly evaluated the effects of opioid treatment for pain was an underpowered crossover study in people with dementia and agitation, in which no clear benefits of the treatment were reported.[86] However, in a further small study to evaluate the use of paracetamol in eight nursing home residents with difficult behaviours, researchers reported decreased behavioural symptoms with successful discontinuation of psychotropic medication in 63% of participants who received analgesic medication.[87]

Summary

Reports in the literature support the value of stepped approaches of analgesia administration to people with dementia, both for the treatment of pain and discomfort and as an important component of the management of behavioural symptoms such as agitation. In agreement with guidelines from the AGS panel on pharmacological treatments, the evidence supports the use of paracetamol as a first-line treatment approach to pain in dementia.[54] However, there are appreciable gaps in the literature that need to be addressed. To date, no large-scale studies have reported the effects of individual analgesics on pain behaviour or intensity. Furthermore, no studies have investigated analgesic treatment in patients with specific types of dementia or focused on how to address different types of pain or common conditions that lead to pain in people with dementia. These are all key omissions, and further disease-specific studies are needed.

The evidence regarding pain treatment in individuals with dementia is restricted to findings from studies on the use of paracetamol and opioids. Research to investigate the benefits or adverse events conferred by NSAIDs, anticonvulsants, antidepressants and other novel analgesics in these individuals are urgently needed. In addition, the effect of analgesia on mood symptoms (such as depression and anxiety) has not been robustly evaluated, and these effects should be considered when making decisions on medication.

Nonpharmacological treatments

Evidence to support the use of nonpharmacological approaches for the treatment of pain in dementia is limited. Studies on the effect of reflexology have provided the most convincing evidence: results from a 4-week crossover trial showed a significant reduction in pain as measured on the CNPI in 21 people with dementia who received reflexology compared with those who received 'friendly care'.[88] A quasi-experimental study also showed some limited benefit of a 4-week music intervention in 15 people with dementia.[89] In addition, promising findings have been reported in studies that utilized a combination of nonpharmacological treatments along with pharmacological treatments similar to those described in the stepped-treatment approaches.[79,85] Small trials in which chiropractic care, Shiatsu therapy, and vitamin D supplementation of diet were assessed did not find any improvement in pain following the intervention.[90–92] A study to explore the benefits of an exercise programme in care home residents with dementia is ongoing.[93]

Conclusions

Pain is a clinically significant problem that must be addressed in the treatment of people with dementia; however, there are important issues that require resolution before clear guidelines on pain management can be formulated. Nursing home patients are at high risk of polypharmacy and associated adverse effects of such treatments. Management of pain should be guided by the best-available evidence on methods to effectively identify pain behaviours, with initial treatment comprising nonpharmacological approaches and, if necessary, administration of the least harmful pain medication at the appropriate dosage. Despite biological evidence to suggest that pain perception is reduced in people with dementia, pain is frequent in these individuals and can be measured by specifically developed and validated assessment tools. A key priority for future research is the development of simple, practical tools to detect and monitor pain in clinical and care settings. To ensure accuracy, the use of more than one instrument for identification of pain is recommended. The value of biomarkers of pain, particularly those related to inflammation, should be considered, as these markers could enhance the accuracy of pain assessment.

The first step towards improved pain management is the appropriate use of pain assessment instruments to identify and monitor pain and response to interventions. Clear evidence supports the value of paracetamol as a stand-alone treatment or as part of a stepped-care approach for the treatment of pain, discomfort and related distress. By contrast, limited evidence is available regarding the value of opioid analgesics; these medications should probably be reserved for the treatment of severe refractory pain. One large RCT, supported by cohort and comparator studies, suggested that stepped

analgesia may be a viable pharmacological treatment approach for people with dementia who experience clinically substantial agitation. The study also showed that paracetamol is a safer alternative medication to atypical antipsychotics. Large RCTs and studies to examine the impact of NSAIDs and other non-opioid pharmacological treatments are a priority to provide a better understanding of the benefits and harms of different treatment options. Further investigation to clarify the altered biology of pain in people with AD and to other dementias is also needed.

Review criteria

Articles selected for inclusion in this Review were searched for using PubMed, MEDLINE, EMBASE, and The Cochrane Library. Full details of the search terms used are provided in Supplementary Box 1 online. Studies included in the Review were fully randomized, prospective treatment studies, longitudinal treatment studies with a comparator group, or open studies with more than 10 participants, in which standardized outcome measures were used with follow-up procedures. Included and excluded studies are summarized in Supplementary Table 2 online.

1. The prevalence of dementia worldwide. *Alzheimer's Disease International* [online], http://www.alz.co.uk/adi/pdf/prevalence.pdf (2008).
2. Scherder, E. *et al.* Pain in dementia. *Pain* **145**, 276–278 (2009).
3. Lin, P. C., Lin, L. C., Shyu, Y. I. & Hua, M. S. Predictors of pain in nursing home residents with dementia: a cross-sectional study. *J. Clin. Nurs.* **20**, 1849–1857 (2011).
4. Bosley, B. N., Weiner, D. K., Rudy, T. E. & Granieri, E. Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. *J. Am. Geriatr. Soc.* **52**, 247–251 (2004).
5. Giron, M. S. *et al.* Sleep problems in a very old population: drug use and clinical correlates. *J. Gerontol. A Biol. Sci. Med. Sci.* **57**, 236–240 (2002).
6. Hall-Lord, M. L., Johansson, I., Schmidt, I. & Larsson, B. W. Family members' perceptions of pain and distress related to analgesics and psychotropic drugs, and quality of care of elderly nursing home residents. *Health Soc. Care Community* **11**, 262–274 (2003).
7. Woolf, A. D. *et al.* Musculoskeletal pain in Europe: its impact and a comparison of population and medical perceptions of treatment in eight European countries. *Ann. Rheum. Dis.* **63**, 342–347 (2004).
8. Soldato, M. *et al.* Non malignant daily pain and risk of disability among older adults in home care in Europe. *Pain* **129**, 304–310 (2007).
9. Brown, S. T. *et al.* Pain experience of the elderly. *Pain Manag. Nurs.* **12**, 190–196 (2011).
10. Maxwell, C. J. *et al.* The prevalence and management of current daily pain among older home care clients. *Pain* **138**, 208–216 (2008).
11. Shega, J. W., Hougham, G. W., Stocking, C. B., Cox-Hayley, D. S. & Greg, A. Pain in community-dwelling persons with dementia: frequency, intensity, and congruence between patient and caregiver report. *J. Pain Symptom Manage.* **28**, 585–592 (2004).
12. van t'Hof, C. E., Zwakhalen, S. M. G. & Hamers, J. P. H. Interventions after diagnosing pain in nursing home residents with dementia: the pilot implementation of an observational pain scale (PACSLAC-D). [Dutch] *Tijdschr. Gerontol. Geriatr.* **42**, 67–78 (2011).
13. Shega, J. W. *et al.* The multidimensional experience of noncancer pain: does cognitive status matter? *Pain Med.* **11**, 1680–1687 (2010).
14. Wu, N., Miller, S. C., Lapane, K., Roy, J. & Mor, V. Impact of cognitive function on assessments of nursing home residents' pain. *Med. Care* **43**, 934–939 (2005).
15. Miro, J. *et al.* Pain in older adults: A prevalence study in the Mediterranean region of Catalonia. *Eur. J. Pain* **11**, 83–92 (2007).
16. Grimby, C. *et al.* Musculoskeletal pain and analgesic therapy in a very old population. *Arch. Gerontol. Geriatr.* **29**, 29–43 (1999).
17. Horn, S. D. *et al.* Description of the National Pressure Ulcer Long-Term Care Study. *J. Am. Geriatr. Soc.* **50**, 1816–1825 (2002).
18. Black, B. S. *et al.* Health problems and correlates of pain in nursing home residents with advanced dementia. *Alzheimer Dis. Assoc. Disord.* **20**, 283–290 (2006).
19. Basbaum, A.I. & Jessell, T. M. The perception of pain in *Principles of Neural Sciences* (eds Kandel, E. R. *et al.*) 472–491 (McGraw-Hill Companies, USA, 2000).
20. Benedetti, F. *et al.* Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration. *Pain* **111**, 22–29 (2004).
21. Benedetti, F. *et al.* Pain threshold and tolerance in Alzheimer's disease. *Pain* **80**, 377–382 (1999).
22. Gibson, S. J. & Helme, R. D. Age-related differences in pain perception and report. *Clin. Geriatr. Med.* **17**, 433–456 (2001).
23. Basbaum, A. I., Bautista, D. M., Scherrer, G. & Julius, D. Cellular and molecular mechanisms of pain. *Cell* **139**, 267–284 (2009).
24. Scherder, E. J., Sergeant, J. A. & Swaab, D. F. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol.* **2**, 677–686 (2003).
25. Scherder, E. J. Low use of analgesics in Alzheimer's disease; possible mechanisms. *Psychiatry* **63**, 1–12 (2000).
26. Scherder, E. J. & Bouma, A. Acute versus chronic pain experience in Alzheimer's disease. *Dement. Geriatr. Cogn. Dis.* **11**, 11–16 (2000).
27. Cornali, C., Franzoni, S., Gatti, S. & Trabucchi, M. Diagnosis of chronic pain caused by osteoarthritis and prescription of analgesics in patients with cognitive impairment. *J. Am. Med. Dir. Assoc.* **7**, 1–5 (2006).
28. Bruckner, G. *et al.* Cortical areas abundant in extracellular matrix chondroitin sulphate proteoglycans are less affected by cytoskeletal changes in Alzheimer's disease. *Neurosci.* **92**, 791–805 (1999).
29. Schmidt, M. L. *et al.* Spinal cord neurofibrillary pathology in Alzheimer disease and Guam Parkinsonism-Dementia. *J. Neuropathol. Exp. Neurol.* **60**, 1075–1086 (2001).
30. Wirths, O., Weis, J., Kayed, R., Saido, T. C. & Bayer, T. A. Age-dependent axonal degeneration in an Alzheimer mouse model. *Neurobiol. Aging* **28**, 1689–1699 (2007).
31. Cole, L. J. *et al.* The impact of Alzheimer's disease on the functional connectivity between brain regions underlying pain perception. *Eur. J. Pain* **15**, e1–e11 (2011).
32. Achterberg, W. P., Pot, A. M., Scherder, E. J. & Ribbe, M. W. Pain in the nursing home: assessment and treatment on different types of care wards. *J. Pain Symptom Manage.* **34**, 480–487 (2007).
33. Closs, S. J., Barr, B. & Briggs, M. Cognitive status and analgesic provision in nursing home residents. *Br. J. Gen. Pract.* **54**, 919–921 (2004).
34. Hutt, E., Pepper, G. A., Vojir, C., Fink, R. & Jones, K. R. Assessing the appropriateness of pain medication prescribing practices in nursing homes. *J. Am. Geriatr. Soc.* **54**, 231–239 (2006).
35. Haasum, Y., Fastbom, J., Fratiglioni, L., Kareholt, I. & Johnell, K. Pain treatment in elderly persons with and without dementia: a population-based study of institutionalized and home-dwelling elderly. *Drugs Aging* **28**, 283–293 (2011).
36. Lövheim, H., Karlsson, S. & Gustafson, Y. The use of central nervous system drugs and analgesics among very old people with and without dementia. *Pharmacoepidemiol. Drug Saf.* **17**, 912–918, (2008).
37. Husebo, B. S., Ballard, C., Sandvik, R., Nilsen, O. B. & Aarsland, D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ.* **343**, d4065 (2011).
38. Bell, J. S. *et al.* Use of strong opioids among community-dwelling persons with and without Alzheimer's disease in Finland. *Pain* **152**, 543–547 (2011).
39. Tse, M. M., Pun, S. P. & Benzie, I. F. Pain relief strategies used by older people with chronic pain: an exploratory survey for planning patient-centred intervention. *J. Clin. Nurs.* **14**, 315–320 (2005).
40. Dosa, D. M., Dore, D. D., Mor, V. & Teno, J. M. Frequency of long-acting opioid analgesic initiation in opioid-naive nursing home residents. *J. Pain Symptom Manage.* **38**, 515–521 (2009).
41. AGS Panel on persistent pain in older persons. The management of persistent pain in older persons. *J. Am. Geriatr. Soc.* **50**, 205–224 (2002).
42. Won, A. B. *et al.* Persistent nonmalignant pain and analgesic prescribing practices in elderly nursing home residents. *J. Am. Geriatr. Soc.* **51**, 193–194 (2003).
43. Dwyer, L. L., Han, B., Woodwell, D. A. & Rechtsteiner, E. A. Polypharmacy in nursing home residents in the United States: results of the 2004 National Nursing Home Survey. *Am. J. Geriatr. Pharmacother.* **8**, 63–72 (2010).
44. Hartikainen, S. A., Mantyselka, P., Louhivuori-Laako, K. A. & Sulkava, R. O. Balancing pain and analgesic treatment in the home-dwelling elderly. *Ann. Pharmacother.* **39**, 11–16 (2005).
45. Stein, C. M. *et al.* Educational program for nursing home physicians and staff to reduce use of non-steroidal anti-inflammatory drugs

among nursing home residents: a randomized controlled trial. *Med. Care* **39**, 436–445 (2001).
46. Ray, W. A. *et al.* Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. *Med. Care* **39**, 425–435 (2001).
47. Manias, E., Gibson, S. J. & Finch, S. Testing an educational nursing intervention for pain assessment and management in older people. *Pain Med.* **12**, 1199–1215 (2011).
48. Merskey, H. Pain terms: a list of definitions and notes on usage. *Pain* **6**, 247–252 (1979).
49. Merskey, H. & Bogduk, N. (Eds) *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* (IASP Press, Seattle, 1994).
50. Closs S. J. A comparison of five pain assessment scales for nursing home residents with varying degrees of cognitive impairment. *Pain Sympt. Mange*. **27**, 196–205 (2004).
51. Martin, R., Williams, J., Hadjistavropoulos, T., Hadjistavropoulos, H. D. & MacLean, M. A qualitative investigation of seniors' and caregivers' views on pain assessment and management. *Can. J. Nurs. Res.* **37**, 142–164 (2005).
52. Morrison, R. S. & Sui, A. L. A comparison of pain and its treatment in advanced dementia and cognitively intact patients with hip fracture. *J. Pain Symptom Manage.* **19**, 240–248 (2000).
53. American Geriatrics Society Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. *J. Am. Geriatr. Soc.* **46**, 635–651 (1998).
54. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J. Am. Geriatr. Soc.* **57**, 1331–1366 (2009).
55. Stolee, P. *et al.* Instruments for the assessment of pain in older persons with cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 319–326 (2005).
56. Hadjistavropoulos, T. *et al.* An interdisciplinary expert consensus statement on assessment of pain in older persons. *Clin. J. Pain* **23**, S1–S43 (2007).
57. Herr, K. Pain Assessment strategies in older patients. *J. Pain* **12**, S3–S13 (2011).
58. Lobbezoo, F., Weijenberg, R. A. & Scherder, E. J. Topical review: orofacial pain in dementia patients. A diagnostic challenge. *J. Orofac. Pain* **25**, 6–14 (2011).
59. Zwakhalen, S. M., Hamers, J. P., Abu-Saad, H. H. & Berger, M. P. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatr*. **6**, 3 (2006).
60. Prkachin, K. M. The consistency of facial expressions of pain: a comparison across modalities. *Pain* **51**, 297–306 (1992).
61. Craig, K. D. & Patrick, C. J. Facial expression during induced pain. *J. Pers. Soc. Psychol.* **48**, 1080–1091 (1985).
62. Ekman, P. Facial Expression and Emotion. *Am. Psychol.* **48**, 384–392 (1993).
63. Kunz, M., Scharmann, S., Hemmeter, U., Schepelmann, K. & Lautenbacher, S. The facial expression of pain in patients with dementia. *Pain* **133**, 221–228 (2007).
64. Teske, K., Daut, R. L. & Cleeland, C. S. Relationships between nurses' observations and patients' self-reports of pain. *Pain* **16**, 289–296 (1983).
65. Snow, A. L. *et al.* Self-reported pain in persons with dementia predicts subsequent decreased psychosocial functioning. *Am. J. Geriatr. Psych.* **17**, 873–880 (2009).
66. Cohen-Mansfield, J. Relatives' assessment of pain in cognitively impaired nursing home residents. *J. Pain Symptom Manage.* **24**, 561–571 (2002).
67. Cohen-Mansfield, J. & Lipson, S. The utility of pain assessment for analgesic use in persons with dementia. *Pain*. **134**, 16–23 (2008).
68. Cohen-Mansfield, J. The relationship between different pain assessments in dementia. *Alzheimer Dis. Assoc. Disord*. **22**, 86–93 (2008).
69. Cohen-Mansfield, J. Pain Assessment in Noncommunicative Elderly persons—PAINE. *Clin. J. Pain*. **22**, 569–575 (2006).
70. Villanueva, M. R., Smith, T. L., Erickson, J. S., Lee, A. C. & Singer, C. M. Pain assessment for the dementing elderly (PADE): reliability and validity of a new measure. *J. Am. Med. Dir. Assoc.* **4**, 1–8 (2003).
71. Herr, K., Bjoro, K. & Decker, S. Tools for assessment of pain in nonverbal older adults with dementia: a state-of-the-science review. *J. Pain Symptom Manage.* **31**, 170–192 (2006).
72. Husebo, B. S., Strand, L. I., Moe-Nilssen, R., Husebo, S. B. & Ljunggren, A. E. Pain in older persons with severe dementia. Psychometric properties of the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale in a clinical setting. *Scand. J. Caring Sci.* **24**, 380–391 (2010).
73. Husebo, B. S. *et al.* Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID): development and validation of a nurse-administered pain assessment tool for use in dementia. *J. Pain Symptom Manage.* **34**, 67–80 (2007).
74. Husebo, B. S. *et al.* Who suffers most? Dementia and pain in nursing home patients: a cross-sectional study. *J. Am. Dir. Assoc.* **9**, 427–433 (2008).
75. Husebo, B. S., Strand, L. I., Moe-Nilssen, R., Husebo, S. B. & Ljunggren, A. E. Pain behaviour and pain intensity in older persons with severe dementia: reliability of the MOBID Pain Scale by video uptake. *Scand. J. Caring Sci.* **24**, 380–391 (2009).
76. Kovach, C., Noonan, P., Griffie, J., Muchka, S. & Weissman, D. The assessment of discomfort in dementia protocol. *Pain Manag. Nurs*. **3**, 16–27 (2002).
77. Pieper, M. *et al.* The implementation of the serial trial intervention for pain and challenging behaviour in advanced dementia patients (STA OP!): a clustered randomized controlled trial. *BMC Geriatr*. **11**, 12 (2011).
78. Hurley, A. C., Volicer, B. J., Hanrahan, P. A., Houde, S. & Volicer, L. Assessment of discomfort in advanced Alzheimer patients. *Res. Nurs. Health* **15**, 369–377 (1992).
79. Kovach, C. R. *et al.* Effects of the Serial Trial Intervention on discomfort and behavior of nursing home residents with dementia. *Am. J. Alzheimers Dis. Other Demen.* **21**, 147–155 (2006).
80. Mattsson, N., Blennow, K., Zetterberg, H. CSF biomarkers: pinpointing Alzheimer pathogenesis. *Ann. NY Acad. Sci.* **1180**, 28–35 (2009).
81. Calutt, N. A., Stiller, C. O., Gustafsson, H., Malmberg, A. B. Elevated substance-like immunoreactivity levels in spinal dialysates during the formalin test in normal and diabetic rats. *Brain Res.* **856**, 20–27 (2000).
82. Manfredi, P. L. *et al.* Opioid treatment for agitation in patients with advanced dementia. *Int. J. Geriatr. Psychiatry* **18**, 700–705 (2003).
83. Chibnall, J. T., Tait, R. C., Harman, B. & Luebbert, R. A. Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. *J. Am. Geriatr. Soc.* **53**, 1921–1929 (2005).
84. Buffum, M. D., Sands, L., Miaskowski, C., Brod, M. & Washburn, A. A clinical trial of the effectiveness of regularly scheduled versus as-needed administration of acetaminophen in the management of discomfort in older adults with dementia. *J. Am. Geriatr. Soc.* **52**, 1093–1097 (2004).
85. Kovach, C. R., Noonan, P. E., Griffie, J., Muchka, S. & Weissman, D. E. Use of the assessment of discomfort in dementia protocol. *Appl. Nurs. Res*. **14**, 193–200 (2001).
86. Hyman, B. T. *et al.* Effect of naltrexone on senile dementia of the Alzheimer type. *J. Neurol. Neurosurg. Psychiatry.* **48**, 1169–1171 (1985).
87. Douzjian, M. *et al.* A program to use pain control medication to reduce psychotropic drug use in residents with difficult behavior. *Ann. Longterm Care* **6**, 174–179 (1998).
88. Hodgson, N. A. & Andersen, S. The clinical efficacy of reflexology in nursing home residents with dementia. *J. Altern. Complement. Med.* **14**, 269–275 (2008).
89. Park, H. Effect of music on pain for home-dwelling persons with dementia. *Pain Manag. Nurs.* **11**, 141–147 (2010).
90. Hawk, C. & Cambron, J. Chiropractic care for older adults: effects on balance, dizziness, and chronic pain. *J. Manipulative Physiol. Ther.* **32**, 431–437 (2009).
91. Robinson, N., Lorenc, A. & Liao, X. The evidence for Shiatsu: a systematic review of Shiatsu and acupressure. *BMC Complement. Altern. Med.* **11**, 88 (2011).
92. Björkman, M., Sorva, A. & Tilvis, R. Vitamin D supplementation has no major effect on pain or pain behavior in bedridden geriatric patients with advanced dementia. *Aging Clin. Exp. Res.* **20**, 316–321 (2008).
93. Volkers, K. M. & Scherder, E. J. The effect of regular walks on various health aspects in older people with dementia: protocol of a randomized-controlled trial. *BMC Geriatr*. **11**, 38 (2011).
94. Melzack, R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* **1**, 277–299.
95. Abbey, J. The Abbey pain scale: a 1-minute numerical indicator for people with end-stage dementia. *Int. J. Palliat. Nurs.* **10**, 6–13 (2004).
96. Hurley, A. C., Volicer, B. J., Hanrahan, P. A., Houde, S. & Volicer, L. Assessment of discomfort in advanced Alzheimer patients. *Res. Nurs. Health* **15**, 369–377 (1992).
97. Feldt, K. S. The checklist of nonverbal pain indicators (CNPI). *Pain Manag. Nurs.* **1**, 13–21 (2000).
98. Warden, V., Hurley, A. C. & Volicer, L. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. *J. Am. Med. Dir. Assoc*. **4**, 9–15 (2003).
99. Morello, R., Jean, A., Alix, M., Sellin-Peres, D. & Fermanian, J. A scale to measure pain in non-verbally communicating older patients: the EPCA-2 Study of its psychometric properties. *Pain* **133**, 87–98 (2007).
100. Lefebvre-Chapiro, S. The DOLOPLUS 2 scale —evaluating pain in the elderly. *Eur. J. Palliat. Care* **8**, 191–194 (2001).
101. Pautex, S., Herrmann, F. R., Michon, A., Giannakopoulos, P. & Gold, G. Psychometric

properties of the Doloplus-2 observational pain assessment scale and comparison to self-assessment in hospitalized elderly. *Clin. J. Pain* **23**, 774–779 (2007).
102. Snow, A. L. *et al.* NOPPAIN: a nursing assistant-administered pain assessment instrument for use in dementia. *Dement. Geriatr. Cogn. Disord.* **17**, 240–246 (2004).
103. van Nispen tot Pannerden, S. C. *et al.* An item response theory-based assessment of the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC). *J. Pain* **10**, 844–853 (2009).
104. Herr, K. A. & Mobily, P. R. Comparison of selected pain assessment tools for use with the elderly. *Appl. Nurs. Res.* **6**, 39–46 (1993).
105. Benedetti, F. *et al.* Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* **121**, 133–144 (2006).
106. Allen, R. S. *et al.* Prescription and dosage of analgesic medication in relation to resident behaviors in the nursing home. *J. Am. Geriatr. Soc.* **51**, 534–538 (2003).
107. Brummel-Smith, K. *et al.* Outcomes of pain in frail older adults with dementia. *J. Am. Geriatr. Soc.* **50**, 1847–1851 (2002).

Acknowledgements
The authors would like to thank the Alzheimer's Society (UK) for supporting the time of Dr Corbett and Professor Ballard to contribute to the review.

Author contributions
A. C. Corbett, B. Husebo and C. Ballard contributed equally to researching data for the article, discussion of content, writing, and review and editing of the manuscript before submission. M. Malcangio and J. Cohen-Mansfield researched data for the article, and contributed to discussions of the content and writing the article. A. Staniland researched data for the article and contributed to discussion of the content. D. Aarsland researched data for the article, and contributed to discussion of the content and review and editing of the manuscript before submission.

Supplementary information
Supplementary information is linked to the online version of the paper at www.nature.com/nrneurol