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Plooij, B.

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Chapter 4

Assessment and management of pain, with particular emphasis on central neuropathic pain, in moderate to severe dementia

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Abstract

In dementia patients, undertreatment of pain, irrespective of its aetiology, is widely recognized; the risk for undertreatment increases with the severity of dementia. We argue, however, that central neuropathic pain is by far the most undertreated type of pain in patients with dementia. Central pain is a type of neuropathic pain that is known to occur in stroke patients and is caused by white matter lesions. Although white matter lesions are also a neuropathological hallmark of dementia, central neuropathic pain has hardly been described in dementia. Therefore, the goal of this review is to address assessment and management of pain, with particular emphasis on central neuropathic pain, in moderate to severe dementia.

Concerning pain assessment, the findings of this review suggest that self-report pain rating scales, in particular the Verbal Rating Scale, the Horizontal Visual Analogue Scale and the Faces Pain Scale can be administered to patients in a more advanced stage of dementia. For those who cannot communicate about pain anymore, pain observation scales are most appropriate. Self-report and pain observation should be combined, if possible. For an overview of assessment tools for pain in nonverbal older persons, we refer to URL: http://prc.coh.org/PAIN-NOA.htm. The review further highlights that behavioural disturbances, e.g. agitation and physical inactivity, as well as autonomic responses, e.g. an increase in blood pressure and heart rate, may contribute to a more reliable assessment of pain. With respect to central neuropathic pain in particular, assessment of sensory abilities (touch, pinprick, temperature, and vibration) and mood (e.g. anxiety), and determination of the presence of a Babinski, accelerated tendon reflexes, and spasticity may contribute to reliable assessment.

Management of pain, not of a central origin, starts with acetaminophen (Paracetamol), which, together with opioids, is the most frequently prescribed analgesic drug in dementia. Non-steroidal anti-inflammatory drugs (NSAIDs) are hardly prescribed in a residential setting. Some authors advise to start with a low dose of opioids. Anti-depressants and antiepileptic drugs appear to have a positive effect on central neuropathic pain. In the review pros and cons of Amitriptyline, Carbamazepine,

Lamotrigine, Gabapentin, and Pregabalin are discussed; a negative effect of these drugs on liver and kidney functions, as well as on cognitive functions in patients who already suffer from cognitive impairment is highlighted. Next to pharmacotherapy, also non-pharmacological treatment strategies such as Transcutaneous Electrical Nerve Stimulation (TENS) may be effective as long as afferent pathways transmitting the electrical stimulus are still intact.

Introduction

There is ample evidence for a high prevalence of pain in older community-dwelling persons. For example, more than 90% of 124 older persons (age mainly between 71 and 90 years) who lived in the community suffered from pain during the month preceding the examination (Brown et al., 2011). In that study the most predominant type of pain was musculoskeletal pain and, next to medication, inactivity was the strategy most applied by the patients to reduce pain. The prevalence of musculoskeletal pain is age-related (Woolf et al., 2010); an increase in the prevalence of musculoskeletal pain has also been observed in community-dwelling older persons during the last four months of life (Smith et al., 2010). Importantly, in this last period of life, those with arthritis suffer from more pain than those without a history of arthritis (Smith et al., 2010).

Musculoskeletal disorders are also the main cause of chronic pain in nursing home residents (Baan et al., 2011), among whom patients with severe dementia (Husebo et al., 2010). Next to arthritis, osteoporosis, old fractures, muscle spasm, and contractures have been observed in patients with severe dementia (Husebo et al., 2010). In addition, peripheral vascular disease, aspiration, and neuropathies were indicated by the medical staff as possible causes for pain in residents with advanced dementia (Black et al., 2006; Ferrell et al., 1995).

As far as we know, very little attention has been paid to ‘central’ pain that may occur in various subtypes of dementia. Central pain is a type of neuropathic pain that is known to occur in stroke patients (Siniscalchi et al., 2012) but has hardly been described in dementia. In patients with

dementia, undertreatment of pain, irrespective of its aetiology and cognitive status, is widely recognized (Morrison and Suit, 2000; Plooij et al., 2012). We argue, however, that central neuropathic pain is by far the most undertreated type of pain in patients with dementia, as the medical staff is less familiar with this type of pain. Appropriate assessment of this type of pain is clinically relevant, as it requires treatment that differs from treatment of other types of pain. The goal of this review is therefore to address assessment and treatment of pain in advanced stages of dementia, with a special focus on central neuropathic pain. However, firstly we will briefly describe central neuropathic pain in stroke and its possible presence in dementia.

Central neuropathic pain

Neuropathic central pain may be caused by a lesion or a disorder that affects afferent somatosensory pathways belonging to the central nervous system, more specifically the spinothalamocortical pathways (Haanpää and Hietaharju, 2010). However, not only damage to the thalamus may provoke central neuropathic pain; a lesion anywhere in the spinal cord or brain may cause this type of pain (Haanpää and Hietaharju, 2010). According to these authors, one of the main causes is a cerebrovascular lesion, e.g. an infarction. Indeed, approximately 35% of stroke patients suffer from post-stroke central neuropathic pain (Siniscalchi et al., 2012). The mechanism underlying central pain is that compared to grey matter, particular white matter is vulnerable for vascular lesions. White matter lesions hamper the afferent transmission of normal somatosensory stimuli to brain areas, for example the thalamus (Hong et al., 2010). By a lack of normal somatosensory information, the thalamus initiates a pain circuit within the central nervous system, resulting in central neuropathic pain, also paraphrased as ‘deafferentiation’ pain.

Of note is that the neuropathology of various subtypes of dementia is characterized by white matter lesions. In particular, white matter lesions are a neuropathological hallmark of subcortical vascular dementia (Scherder, Sergeant and Swaab, 2003; Tomimoto, 2011), the most prevalent subtype of vascular dementia. Indeed, results of the one available study on pain in patients with possible vascular dementia suggest

an *increase* in pain experience, compared to older persons without vascular dementia (Scherder et al., 2003). We suggest that this increase in pain experience might be a reflection of central neuropathic pain. This suggestion is supported by the finding that cognitively impaired nursing home residents with diabetes or hypertension, both risk factors for white matter lesions, showed a higher risk for pain (Achterberg et al., 2007). Central neuropathic pain may also occur in Alzheimer's disease and frontotemporal dementia as the neuropathology of both subtypes also consists of white matter lesions (Scherder, Sergeant and Swaab, 2003).

Pain assessment

Self-report pain rating scales

To measure pain intensity and pain affect, numerous self-report pain rating scales are available, i.e. visual analogue scales (VASs; horizontal or vertical), the Verbal Descriptor Scale (VDS), the Numeric Rating Scale (NRS), the Faces Pain Scale (FPS), the Color Pain Assessment Scale, and the Pain Thermometer (Jones et al., 2007). Other self-report pain scales include the Functional Pain Scale, the Present Pain Intensity, and the Global Pain Assessment (Cohen-Mansfield, 2008). Obviously, the ability to indicate pain by self-report rating scales depends on the cognitive functioning of the patient with dementia. For example, dementia patients with advanced cognitive impairment appeared not to be able anymore to answer to pain-related questions (Cohen-Mansfield, 2008). In that study participants had a score of < 9 on the Mini-Mental State Examination (MMSE), a test that measures global cognitive functioning by evaluating orientation in time and place, registration, recall, attention and calculation, language and praxis, and visuoconstructive abilities (maximum score: 30) (Folstein et al., 1975). On the other hand, self-report of pain in an even more advanced stage of dementia may still be possible. The Verbal Rating Scale, the Horizontal Visual Analogue Scale and the Faces Pain Scale were administered to, among others, patients with dementia with a MMSE score < 6 (n=67); forty-nine per cent understood the concept of at least one of the three scales (Pautex et al., 2006). For further details concerning psychometric properties of the VAS, the 21-point NRS, the VDS, the 11-

point Verbal Numeric Rating Scale (VNS), and the FPS, please see Herr et al. (2004; 2010).

Observation scales

Particularly in more advanced stages of dementia, patients are no longer able to understand and respond to even simple questions about pain (Zwakhalen et al., 2006). For those who cannot communicate about pain anymore, observation scales are more reliable tools to assess pain (Zwakhalen et al., 2006). Zwakhalen and co-workers (2006) reviewed the psychometric qualities of 12 pain observation scales: 1) DOLOPLUS2, 2) L'Echelle Comportementale pour Personne Agées (ECPA), 3) L'Echelle Comportementale simplifiée (l'ECSECS, 4) Observational Pain Behavior Tool, 5) Checklist of Non-verbal Pain Indicators (CNPI), 6) Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), 7) Pain Assessment in Advanced Dementia (PAINAD), 8) Pain Assessment in Dementing Elderly (PADE), 9) Rating Pain in Dementia (RaPID), 10) The Abbey Pain Scale; 11) The Non-Communicative Patient's Pain Assessment Instrument (NOPPAIN), and 12) Pain Assessment Scale for Use with Cognitively Impaired Adults. The results of that review showed that the PAINAD, the PACSLAC, the DOLOPLUS2, and the ECPA showed the best, i.e. *moderate*, psychometric quality. After adding two criteria, i.e. detection of subtle behavioural changes and applicability by for example the nursing staff, the PACSLAC and the DOLOPLUS2 are recommended (Zwakhalen et al., 2006). In a later study, the psychometric qualities of the CNPI were compared with those of the PAINAD (Ersek et al., 2010). The authors conclude that both scales could be used to assess pain during movement but are inadequate to measure pain ‘at rest’, limiting the clinical use of both scales. For further details concerning pain observation scales, we refer to an overview of assessment tools for pain in nonverbal older adults at the website of the City of Hope Pain and Palliative Care Resource Center (http://prc.coh.org/PAIN-NOA.htm).

Self-report rating scales combined with observation scales

Little agreement exists between self-report pain ratings and pain ratings obtained by observation (Cohen-Mansfield, 2008). This disagreement holds for the intensity of pain in particular. More specifically, the medical staff estimates patient's pain intensity lower than indicated by the patient, whereas the family thinks the patient is suffering from more pain than indicated by the patient; both medical staff and family are very well able to determine the *presence* of pain (Herr et al., 2006). It has also been observed that the patient's pain, assessed by self-report, is lower than observed by behavioural assessment (Horgas et al., 2009). Considering the disagreement between self-report and observation, both types of instruments, i.e. self-report pain rating scales and observation scales, should be applied; of course, the patient's understanding of the meaning of the self-report rating scales is a prerequisite.

Behavioural disturbances as indicators of pain

Particularly in patients with severe dementia, chronic pain provokes behavioural disturbances (Cipher et al., 2006). Compared to chronic pain patients with mild and moderate dementia, those with severe dementia showed a higher number and a higher frequency of behavioural disturbances such as physical combativeness, agitation, distressing repetitive behaviours, delusional territorial behaviours, socially disruptive behaviours, and wandering (Cipher et al., 2006). The authors emphasize that irrespective of the stage of dementia, anhedonia, depressive symptoms, withdrawal, and a decrease in the level of physical activity, appetite, and weight may point to the presence of pain.

Autonomic responses to pain

The question arises whether in older people with dementia autonomic responses to pain, e.g. changes in skin conductance, changes in blood pressure, or changes in heart rate are still present and if so, if these responses are present independent of the stage of dementia (Plooij et al., 2011). A limited number of studies on this topic are available. In one study, heart rate responses in reaction to a venipuncture were similar in

both patients with Alzheimer's disease and older persons without dementia (Porter et al., 1996). However, the autonomic responses showed a positive relationship with the level of cognitive functioning, i.e. the lower the cognitive functioning, the lower the autonomic responses (Porter et al., 1996). Similar findings were reported in a later study (Benedetti et al., 2004). Autonomic responses to pain in Alzheimer patients do depend on the intensity of the painful stimulus (Rainero et al., 2000). They found that a strong (twice the pain threshold) electrical stimulus provoked a more profound heart rate increase in patients with Alzheimer's disease, albeit less than in those without dementia; the increase in blood pressure during this stimulation was even similar to people without dementia.

One should bear in mind that an increase in blood pressure and heart rate may only be indicative for (severe) pain when the patient is in general familiar with lower values. The absence of an increase in heart rate and blood pressure should not be interpreted as indicative for no pain. For example, absence of autonomic responses to pain may be caused by cardiovascular medication (Plooij et al., 2011). It is known that beta-blockers and calcium channel blockers, medication that is frequently used by older people, lower blood pressure and heart rate (Basile, 2004; Ram, 2010).

Assessment of central neuropathic pain

Clinical features of central neuropathic pain may contribute to its diagnosis: the pain is localized in one side of the body (face, upper and lower limb) and typified as burning, aching, and pricking. The pain could be constant and spontaneous. An important characteristic of central neuropathic pain is allodynia (Haanpää and Hietaharju, 2010). Allodynia means that the patient experiences severe pain that is provoked by sensory stimuli that are normally not painful at all, e.g. light touch or a thermal stimulus (Haanpää and Hietaharju, 2010). Testing of sensory abilities (touch, pinprick, temperature, and vibration) should therefore be part of the neurological examination (Haanpää and Hietaharju, 2010). Also emotions like anxiety may provoke central neuropathic pain (Lovick, 2008); in other words, one should be extra alert to pain in anxious patients. As central neuropathic pain is a consequence of a central nervous system

lesion, the presence of a Babinski, accelerated tendon reflexes, and spasticity should be controlled for (Haanpää and Hietaharju, 2010).

Pain management

It is widely recognized that patients with dementia are at risk of undertreatment of pain (Morrison and Siu, 2000), particularly in the more advanced stages (Scherder et al., 2005). A recent Swedish study however showed that undertreatment of pain in patients with dementia is not a consistent finding; they found even the opposite (Haasum et al., 2011). In that study, 46% of the patients with dementia used analgesia, compared to 25% of the older persons without dementia. The most frequently prescribed analgesic drug was acetaminophen (Paracetamol), followed by non-steroidal anti-inflammatory drugs (NSAIDs), although the latter was hardly prescribed in the residential setting (Haasum et al., 2011). Also both Paracetamol and opioids were prescribed more commonly than NSAIDs in persons with dementia in this study (Haasum et al., 2011). Concerning dosages, patients with dementia used a higher dosage of Paracetamol but a lower dosage of opioids than older persons without dementia. As musculoskeletal disorders (rheumatic disorders, osteoporosis, osteoarthritis, hip fractures) were the most prevalent pain-related conditions, Paracetamol is justified as the preferred analgesic in this population (Haasum et al., 2011), and is, probably for that reason, recommended as the most appropriate analgesic drug to start pain treatment.

General recommendations for clinicians who want to start pain treatment for a nonverbal patient suspected of pain emerge from a paper of Herr and co-workers (2006). They suggest an analgesic trial that starts with Paracetamol 4 times a day (each time 500 mg to 1000 mg), for mild to moderate pain. In the absence of the expected treatment effect, a single low dose, short-acting opioid (e.g., hydrocodone, oxycodone, or morphine) should be considered; the dose reduction for older persons should be 25% - 50%. If a treatment effect (e.g. an improvement in pain-related behavioural disturbances) remains absent, they suggest titrating dose upward by 25% to 50% and continuing to do so till a treatment effect is observed. In case of moderate to severe pain, Herr and co-workers (2006) advise to begin the

treatment with a low dose of opioids. In a 104-year old patient with Alzheimer's disease and agitation-related pain due to musculoskeletal problems, acetaminophen was ineffective (Passmore, 2011). However, a sublingual concentration of 50 micrograms/mL sufentanil, an ultra-brief acting opioid, administered 5 minutes before nursing care, made agitation as a response to care-related pain, disappear. For further reading about guidelines for pain treatment in patients with dementia, the paper of Herr et al. (2006) is recommended.

As far as we know, guidelines for pain treatment in patients with dementia in general do not particularly relate pain medication to the *type* of pain. We would plead for such an adjustment as for example central neuropathic pain does not respond to Paracetamol.

Central neuropathic pain

Anti-depressants and anti-convulsants appear to have a positive effect on central neuropathic pain (Haanpää and Hietaharju, 2010). According to these authors, Amitriptyline, an anti-depressant, appears to be effective for post-stroke central pain; start dosage is 10-25 mg in the evening, and subsequently increased in steps of 10-25 mg to 50-150 mg/day. Carbamazepine, an anti-convulsant with a start dosage of 100 mg/day, and during a short period of a few days increased up to 400-800 mg/day in steps of 100 mg, may also be effective for the relief of central pain. However, others found no effects of 800 mg/day Carbamazepine on central post-stroke pain, and titration should take place carefully considering side-effects (Siniscalchi et al., 2012). In contrast, Lamotrigine (200 mg/day), another anti-convulsant, did reduce post-stroke central pain (Siniscalchi et al., 2012). Gabapentin, also an anti-convulsant, could be administered with a start dosage of 300 mg/day in the evening, and subsequently increased to an effective dosage of 900-3600 mg/day, in steps of 300 mg daily or every other day. The total daily dosage should be divided into three daily administrations (Haanpää and Hietaharju, 2010). Gabapentin may cause serious side effects such as dizziness, drowsiness, and weight gain, complicating its long-term use (Siniscalchi et al., 2012). The anti-convulsant Pregabalin (150–600 mg/day) improved particularly secondary outcome measures, e.g. sleep and anxiety (Siniscalchi et al., 2012).

The above-mentioned adverse effects are characteristic for drugs like antiepileptic drugs (Perucca et al., 2006). Therefore, the authors emphasize the importance of re-evaluation after a certain period of medication (Perucca et al., 2006). Within this scope, Siniscalchi and co-workers (2012) warn for a drug – drug interaction in older persons who are taken multiple medications. For that reason, antiepileptic drugs such as Carbamazepine may not be administered to older persons, as for example Carbamazepine may interact with Paracetamol, causing a dysfunction of the liver and kidney (Jickling et al., 2009). In addition, the functioning of the liver (metabolism of drugs) and kidney (excretion of drugs) may show an age-related decline, further supporting a cautious prescription of antiepileptic drugs in older persons (Siniscalchi et al., 2012). In case of (suspect of) hepatic and renal dysfunction, a lower dosage of Amitriptyline (Murphy, 2005), Lamotrigine (Faught, 1999), Gabapentin (Zand et al., 2010), and Pregabalin (Prescrire Int, 2005) is recommended.

The prescription of antiepileptic drugs in patients with dementia requires even more cautiousness considering the negative effect of these drugs on cognitive functions. It is known that Amitriptyline may impair memory because of its anticholinergic property (Knegtering et al., 1994). Not all antiepileptic drugs influence cognition to the same extent and in the same way though. For example, Carbamazepine has a more negative effect on cognition – in most cases a slowing of information processing speed – than Gabapentin (Mendez and Lim, 2003). In contrast, Pregabalin and Lamotrigine may improve patient's cognitive functioning (Siniscalchi et al., 2012). Other adverse effects of antiepileptic drugs in dementia include a confused state, ataxia, deterioration in visual functions, and cardiac arrhythmias (Mendez and Lim, 2003).

A final important point is that information about the time needed for one of these drugs to be effective and about the moment and way the treatment should be terminated, is lacking (expert opinion).

Next to pharmacotherapy, non-pharmacological treatment strategies such as Transcutaneous Electrical Nerve Stimulation (TENS) may be effective; a prerequisite for effective TENS is that afferent pathways transmitting the electrical stimulus are still intact (Haanpää and Hietaharju, 2010).

Conclusions

- Although musculoskeletal disorders are considered the main cause of pain in patients with dementia, central neuropathic pain should be considered as another main cause of patient's discomfort.
- Central neuropathic pain is known as post-stroke pain, but may also occur in patients with subcortical vascular dementia, Alzheimer's disease, and frontotemporal dementia.
- In view of the disagreement between pain scores obtained by self-report and observation, it is recommended to apply both types of instruments.
- Behavioural disturbances can be indicators for pain, particularly in severe dementia where other instruments to assess pain, e.g. self-report pain rating scales, are not applicable anymore. An example of a behavioural disturbance that is often overlooked as an indicator for pain is *physical inactivity*.
- An increase in heart rate and blood pressure may point to the presence of *severe* pain in patients with Alzheimer's disease, but only when lower baseline measures are available.
- Traditional neurological examination (touch, pinprick, temperature, vibration, reflexes and examination of muscle tone) may contribute to the diagnosis of central neuropathic pain.
- One should be more alert to the presence of (central neuropathic) pain in anxious patients.
- Insight into the *type* of pain contributes to a more effective pain treatment; Paracetamol is not effective in patients suffering from central neuropathic pain.
- Anti-depressants and anti-convulsants should be taken into consideration when treating central neuropathic pain.

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