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Abstract

Dementia diseases, led by Alzheimer's disease (AD), are among the most common and serious conditions affecting the elderly. The number of people suffering from Alzheimer's disease is increasing every year. Among these individuals, a significant portion experiences chronic pain, the diagnosis of which poses a major challenge due to communication difficulties with the patients suffering from Alzheimer's disease. The objective of this publication is to provide an overview of the available methods for diagnosing and treating pain in patients with

Alzheimer’s disease. The article presents the studies that utilized neuroimaging diagnostics and scales used to assess the severity and impact of pain on daily functioning, as well as the medications used. Neuroimaging studies indicate that while pain pathways are preserved in the early stages of Alzheimer's disease, the response to pain stimuli diminishes in more advanced stages, potentially necessitating higher doses of analgesics in many AD patients. Effective treatment of chronic pain is crucial for improving the quality of life of patients, yet its diagnosis still presents many challenges due to communication difficulties with these individuals, the lack of precise scales, assessment methods, and the small number of individuals included in the studies.

Keywords: dementia, Alzheimer's disease, chronic pain, treatment, pain assessment tools, indicator of pain

Introduction

In the aging population of industrialized countries, dementia diseases, led by Alzheimer's disease, are among the most serious diseases of the elderly (Leszek J., 2012). It is estimated that approximately 50 million people worldwide suffer from dementia (Liao Y.J., Jao Y.J., et al., 2023). According to the latest research, it is estimated that by 2050 the number of dementia patients in Europe will double and worldwide will triple (Scheltens P., et al., 2021). Pharmacological treatment of Alzheimer's disease is limited to symptom relief. To this end, cholinesterase inhibitors-donepezil, rivastigmine, and galantamine along with the NMDA receptor antagonist-memantine are used. These medications do not halt disease progression but only improve cognitive functions and daily functioning (Zheng Q., Wang X., 2025). The risk of pain and neurodegenerative diseases increases with age. The neurodegenerative changes present in Alzheimer's disease may affect areas of the brain related to the perceptual and cognitive processes underlying pain (Scherder E.J., Bouma A., 2000).

Chronic pain

Chronic pain is defined as pain lasting more than 3 months. Disturbances in the pain conduction system lead to hypersensitivity that prevents proper conduction, perception and response to pain stimuli (Domżał M.T., 2008). The prevalence of chronic pain in patients with Alzheimer's disease is estimated at 46% (van Kooten J., Binnekade TT, et al., 2016). Around

one-third of people with dementia, despite regular use of analgesics, experience moderate or severe pain (Liao Y.J., Jao Y.J., et al., 2023). Pain is commonly linked to the musculoskeletal, gastrointestinal, and cardiovascular systems, as well as to urinary tract infections and pressure ulcers. Orofacial pain is also a commonly occurring condition (Achterberg W.P., et al 2013). Patients with Alzheimer's disease are often accompanied by neuropsychiatric symptoms such as agitation, depression, aggression, apathy and sleep disturbance. It has been suggested that one of the triggers for neuropsychiatric symptoms may be undiagnosed and untreated pain (Husebo B. S., et al., 2016).

This issue may, in fact, affect a significantly larger group of patients who, due to communication impairments, are often unable to report their symptoms.

Brain Regions Degeneration

The locus coeruleus is one of the earliest regions of the brain affected by neurodegeneration during the development of Alzheimer's disease. Autopsy results of patients indicate a loss of neurons in this area in the range of 50-60%, and the rate of loss is correlated with the duration of the disease. Neuroimaging studies have demonstrated a relationship between the deterioration of cognitive functions in patients with chronic pain and the volume of gray matter in brain regions affected by early degenerative changes in Alzheimer's disease (Cao S., et al., 2019). Also in Alzheimer's disease, the striatum is heavily affected. As studies using fMRI show, it can be assumed that individuals with mild and moderate Alzheimer's disease have increased striatal activation in response to pain. In the case of advanced Alzheimer's disease, this activation is relatively reduced. As a result, behavioral changes in mild and moderate Alzheimer's disease are more pronounced, while in advanced Alzheimer's disease, they may be normal or subdued. As experimental studies show, individuals with Alzheimer's disease likely require higher doses of painkillers than healthy individuals to achieve a therapeutic effect. This conclusion was drawn based on an experimental study that demonstrated that endogenous expectations and the placebo mechanism are weakened in individuals with Alzheimer's disease (Achterberg W.P., et al., 2013). In patients with Alzheimer's disease, increased blood-brain barrier permeability is often associated with elevated albumin levels in the cerebrospinal fluid, which also correlates with disease progression (Banks W.A., 2011). That may impact the effectiveness of centrally acting pain medications, such as morphine (Achterberg W.P., et al., 2013).

The link between chronic pain and Alzheimer's disease

Pain intensity has been shown to correlate with the degree of dementia (Cao S., et al., 2019). This conclusion is based on a study conducted by Schreder EJ and colleagues, which involved 20 elderly people without dementia and 19 people with probably early-stage Alzheimer's disease. Both groups of subjects suffered from arthrosis. Pain intensity and impact were assessed using the Analogue Color Pain Intensity Scale, the Faces Pain Scale (FPS) and the Number of Words Chosen Affective Scale (NWC-A). The level of depression and anxiety was assessed using special questionnaires, whereas neuropsychological tests were used to assess executive functions and memory. Research results suggest that in people with normal cognitive function there are no significant correlations between cognitive abilities and the degree of pain intensity. However, a positive correlation is observed between cognitive impairment and pain severity (Scherder E.J., et al., 2008).

Pain is a primary factor causing agitation and mood disturbances in individuals with dementia. As a consequence, this may lead to the excessive use of antipsychotic medications, which carry a risk of adverse effects. In dementia, the sensory cortex remains relatively unaffected pathologically until the final stage of the disease. The pain threshold may be similar to or higher than that of healthy individuals. Patients with Alzheimer's disease and reduced frontal lobe function showed a decreased response to placebo in the open-hidden model and required higher doses of analgesics (Lawn T., et al., 2020).

Results of fMRI studies in patients with Alzheimer's disease

To assess pain and functional brain MRI response, a study was conducted in 14 patients with early-stage Alzheimer's disease. The control group consisted of 15 healthy people. Participants did not report any prior pain and were not taking medication during the study. They also did not suffer from diseases that could affect the perception of pain. The test consisted in mechanical pressure on the nail of the right hand with a stimulus lasting 5 seconds. The results of the study suggest that activity in both the medial and lateral spinal pain pathways was preserved in patients with Alzheimer's disease. Alzheimer's patients showed highest amplitude and duration of pain-related activity in regions responsible for sensory, affective and cognitive processing. In addition, they showed a higher tolerance to the presence of a pain stimuli (Cole L.J., et al., 2006). The results of the study allow to draw

conclusions that patients suffering from Alzheimer's disease, although they do not communicate about the existing pain, feel it to a significant extent.

Treatment of pain in patients with Alzheimer's disease

Competent pain assessment is essential for effective pain management. It should consider parameters such as location, intensity, behavior, cognition, and social aspects. In individuals with Alzheimer's disease, accurate pain assessment is particularly challenging due to communication difficulties, and improper pain management can lead to harmful health consequences. Paracetamol/acetaminophen remains the primary analgesic used in advanced dementia for the treatment of mild to moderate pain. Despite limited evidence, paracetamol is still considered a safe and effective first-line treatment for pain management in these patients. (Achterberg W.P., et al., 2020). In another study by Chibnal et al. which involved 25 people with moderate to severe dementia, Dementia Care Mapping and Cohen-Mansfield Agitation Investors were used to assess the effect. It was noticed that patients were more active during the treatment, more willing to integrate and spend time in society. However, paracetamol did not reduce the feeling of anxiety and did not reduce the use of emergency psychotropic drugs. Effectiveness in assessing pain intensity has not been studied with a validated pain assessment tool (Husebo B.S., et al., 2016). Another double-blind, crossover study conducted by Paolo L. Manfredi and colleagues, involved 47 participants with advanced dementia and severe agitation despite treatment with psychotropic drugs. For the first 4 weeks, study participants received a placebo, followed by a long-acting oxycodone preparation for the next 4 weeks. Efficacy was assessed using the Cohen Manifield Agitation Inventory - a scale that is a recognized tool for assessing aggressive behavior in people with dementia. Among the participants in the study, 25 of them completed the two phases of the study. The median age of these patients was 85.5 years. Data analysis of these patients and patients <85 years of age showed no significant differences in agitation between the placebo and opioid phases. The 13 patients who completed the study and were over 85 years of age had less agitation at the end of the opioid phase. This may prove the effectiveness of long-acting opioids in reducing agitation that is difficult to control with psychotropic drugs in very elderly patients (over 85) with advanced dementia (Manfredi P.L., et al., 2003).

Due to the pathologies present in the central nervous system that prevent the activation of descending cholinergic pain control pathways, when selecting drugs from the group of non-steroidal anti-inflammatory drugs, those with peripheral action, such as etoricoxib, should be

taken into account. Drugs with a central effect for exemple ketoprofen, dexketoprofen, are avoided (Wordliczek J., et al., 2018).

Based on the conducted study performed by Ballard and colleagues, among individuals with dementia, buprenorphine was found to be poorly tolerated. Its use was associated with a higher prevalence of psychiatric adverse events compared to studies conducted among patients without dementia. Buprenorphine administration was linked to decreased daytime activity in the subjects. Individuals with dementia are susceptible to adverse events even at the lowest dose of the drug, and therefore, they should be continuously monitored, especially when also taking antidepressant medications (Erdal A., et al., 2018).

Agitation is one of the neuropsychiatric symptoms that significantly affects the quality of life in patients with dementia. Citalopram was found to be the only effective antidepressant in the management of agitation symptoms in patients with dementia. Further research is required to evaluate the use of citalopram, incorporating larger patient populations and considering other factors such as treatment duration, dosing regimens, and potential drug interactions with concomitant medications (Chen K., et al., 2023).

Postmortem brain studies conducted on individuals suffering from Alzheimer's disease have shown weakened binding to μ and δ opioid receptors. This suggests that in these patients, opioid-induced analgesia, mediated by the central nervous system, may be altered (Lawn T., et al., 2021).

For the treatment to be effective, it is also essential to recognize the point at which a therapeutic response occurs. According to Cohen-Mansfield and Jensen, pain assessment tools should be able to identify individuals whose pain will decrease after receiving analgesic treatment (Achterberg W.P. et al., 2013).

Pain assessment tools

In patients with Alzheimer's disease, due to difficulties in verbally communicating pain, specially dedicated scales have been developed to assess pain.

One of them is the Pain Assessment in Impaired Cognition scale (PAIC15). This scale consists of five items, each related to facial expressions, body movements, and vocalizations, respectively. The 15 items being assessed have demonstrated high psychometric quality and clinical usefulness (Kunz M., et al., 2019).

During one of the studies, attention was drawn to one of the limitations of the scale, which was the inclusion of patients experiencing acute pain in the experimental study, whereas

individuals with Alzheimer's disease more frequently suffer from pain associated with chronic conditions. (Defrin R., et al., 2021)

Another very popular tool is the Visual Analogue Scale (VAS) which consists of a line where patients mark their pain intensity, typically ranging from "no pain" to "worst possible pain,", then the specialist, measure the distance between left endpoint and patient mark (Gillian Z. Heller et. al., 2016). One of the studies involved the use of several types of VAS scales, including the Coloured Analogue Scale (CAS), the Faces Pain Scale (FPS), and the Facial Affective Scale (FAS), in patients at different stages of dementia as well as in elderly adults without dementia. The results showed that older adults without dementia understood the principles of the scales better than those with Alzheimer's disease. Nondemented elderly persons described their pain and its impact on well-being as significantly more intense than patients with Alzheimer's when using the VAS scale. These results indicate that the VAS scale can greatly facilitate pain assessment, but only in Alzheimer's patients who fully understand how it works (Scherder E.J., Bouma A., 2000). However, due to communication difficulties with these patients and the uncertainty of whether they grasp its purpose, it cannot be used as the sole tool for pain assessment.

Another tool used for pain assessment in patients with dementia is the electronic Pain Assessment Tool (ePAT). This tool utilizes facial micro-expression recognition technology to detect the presence of pain. Furthermore, ePAT records pain-related behaviors across five domains: movement, voice, activity, body, and behavior. The tool automatically analyzes facial expressions, enabling objective pain assessment and providing reproducible evidence of pain occurrence. The main limitations of this tool are its limited availability and the relatively small number of patients in whom it has been implemented so far (Atee M., et al., 2017).

DOLOPLUS-2 is a behavioral pain assessment scale designed for elderly individuals with impaired verbal communication. It evaluates five somatic items, two psychomotor items, and three psychosocial items as indicators of pain. Version 2 of the Japanese DOLOPLUS-2 scale was tested on six patients and 31 nurses. Case study analysis revealed that pain scores were high only when patients clearly exhibited signs of pain. The results of this study suggest that Version 2 of the Japanese DOLOPLUS-2 can be used to assess pain in patients with Alzheimer's disease (AD); however, the final version of the scale requires validation in a larger cohort of patients (Ando C., et al., 2010).

The Abbey Pain Scale is a tool used to assess the intensity of pain in individuals with advanced-stage dementia. The scale evaluates six parameters: vocalization, facial expression, change in body language, behavioral change, physiological change, and physical change. Each parameter is scored based on its severity on a scale from 0 to 3 points. The maximum possible score on the above scale is 18 points. A score greater than 3 points indicates mild pain, a score between 8 and 13 points indicates moderate pain, and a score greater than 14 points indicates severe pain. Unfortunately, despite the analysis of some psychometric aspects, the current version of this pain assessment scale still exhibits shortcomings in terms of validity and reliability (Zwakhalen S.M., et al, 2006).

Heart Rate as an Indicator of Pain in Dementia

Currently, heart rate measurements are frequently used by doctors to assess pain intensity. The assumption is that as a patient's pain increases, their heart rate should also rise. However, this principle has not yet been fully studied.

To determine the relationship between pain intensity and heart rate, a study was conducted in which pain receptors were stimulated by placing the participant’s hand in a container of hot water. Heart rate was measured two minutes before the test and during the procedure.

The results showed an 11% increase in heart rate after a two-minute rest period. Additionally, differences in heart rate changes were observed depending on the participant's gender. The study did not find a correlation between pain intensity and heart rate increase among women, indicating the need for further research to establish the precise relationship between heart rate measurements and pain intensity (Tousignant-Laflamme Y. et al., 2005).

Conclusions

Researchers continues to develop the best possible pain assessment method for people with advanced dementia. Most of the currently available methods are based on the assumptions and recommendations of the Panel of the American Geriatric Society (AGS), based on the fact that pain is expressed mainly through facial expressions. Untreated pain can lead to crying or irritability. However, there is a difficulty in the correct interpretation of the above behaviors. It is not certain whether they are caused by the accompanying pain or whether they are caused by the dementia process. It should be noted that most scales have been validated for the presence of pain, not for its intensity (Husebo B. S., et al., 2016).

So far, only a few studies have investigated the reactivity of tools, defined as the ability of these instruments to detect changes over time for pain assessment in individuals with dementia and elderly patients who are unable to communicate verbally. The most sensitive tools for self-report, informant assessment, and observational evaluation of analgesic treatment with both non-opioid and opioid medications were the Pain Assessment for the Dementing Elderly and the Pain Assessment Instrument for Noncommunicative Elderly. It is therefore necessary to continue searching for tools and methods that will allow for a more accurate assessment of pain intensity.

In the cited works, the small number of respondents is noteworthy. Studies conducted on larger groups would increase the credibility of the results obtained, and perhaps allow for drawing additional conclusions.

Due to frequent communication difficulties, especially among patients in a more advanced stage of the disease, there is a high probability that chronic pain occurs in a much larger group of people who, however, are unable to communicate it verbally. The results of neuroimaging studies provide indisputable information on the occurrence of pain in patients suffering from Alzheimer's disease and should be the basis for the need for appropriate pain management in these people. Physiological pain indices are the most frequently observed and most important parameters in the assessment of pain in patients unable to self-report their pain. Of these, an increase in heart rate appears to be the most important (Gutysz-Wojnicka A., et al., 2014).

The increase in heart rate may prove to be an easy parameter to assess in an outpatient setting, and its continuous monitoring using mobile devices will enable effective pharmacological intervention; however, it is crucial to conduct further studies to determine the exact correlation between pain intensity and heart rate value.

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References:

1. Leszek J. Choroba Alzheimera: obecny stan wiedzy, perspektywy terapeutyczne, Polski Przegląd Neurologiczny, 2012, tom 8, nr 3

2. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet. 2021 Apr 24;397(10284):1577-1590. doi: 10.1016/S0140-6736(20)32205-4. Epub 2021 Mar 2

3. Scherder EJ, Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease. Gerontology. 2000 Jan-Feb;46(1):47-53. doi: 10.1159/000022133.
4. Domżał TM. Ból przewlekły problemy kliniczne i terapeutyczne, Polski Przegląd Neurologiczny, 2008, tom 4, nr 1

5. van Kooten J, Binnekade TT, van der Wouden JC, Stek ML, Scherder EJ, Husebø BS, Smalbrugge M, Hertogh CM. A Review of Pain Prevalence in Alzheimer's, Vascular, Frontotemporal and Lewy Body Dementias. Dement Geriatr Cogn Disord. 2016;41(3-4):220-32. doi: 10.1159/000444791. Epub 2016 May 10

6. Cao S, Fisher WD, Yu T, Dong H. The link between chronic pain and Alzheimer's disease, Cao et al. Journal of Neuroinflammation (2019) 16:204. doi: 10.1186/s12974-019-1608-z.

7. Scherder EJ, Eggermont L, Plooij B, Oudshoorn J, Vuijk PJ, Pickering G, Lautenbacher S, Achterberg W, Oosterman J. Relationship between chronic pain and cognition in cognitively intact older persons and in patients with Alzheimer's disease. The need to control for mood. Gerontology. 2008;54(1):50-8. doi: 10.1159/000113216. Epub 2008 Jan 10

8. Cole LJ, Farrell MJ, Duff EP, Barber JB, Egan GF, Gibson SJ. Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. Brain. 2006 Nov;129(Pt 11):2957-65. doi: 10.1093/brain/awl228. Epub 2006 Sep 2

9. Husebo BS, Achterberg W, Flo E. Identifying and Managing Pain in People with Alzheimer's Disease and Other Types of Dementia: A Systematic Review. CNS Drugs. 2016 Jun;30(6):481-97. doi: 10.1007/s40263-016-0342-7

10. Herr K, Coyne PJ, Ely E, Gélinas C, Manworren RCB. Pain Assessment in the Patient Unable to Self-Report: Clinical Practice Recommendations in Support of the ASPMN 2019 Position Statement. Pain Manag Nurs. 2019 Oct;20(5):404-417. doi: 10.1016/j.pmn.2019.07.005. Epub 2019 Oct 12.

11. Manfredi PL, Breuer B, Wallenstein S, Stegmann M, Bottomley G, Libow L. Opioid treatment for agitation in patients with advanced dementia. Int J Geriatr Psychiatry. 2003 Aug;18(8):700-5. doi: 10.1002/gps.906.

12. Wordliczek J, Woroń J, Targońska-Stępniak B, Tarnacka B, Malec-Milewska M. Leczenie bólu zapalnego – problem interdyscyplinarny widziany oczami reumatologa, neurologa, rehabilitanta, specjalisty medycyny bólu i farmakologa klinicznego Treatment of inflammatory pain – an interdisciplinary problem from the perspective of a rheumatologist,

neurologist, physiotherapist, pain specialist and clinical pharmacologist, Ból 2018, Tom 19, Nr 4, s. 11–26, DOI: 10.5604/01.3001.0013.2753

13. Gutysz-Wojnicka A, Dyk D, Ozga D, Cudak E. Pozawerbalne wskaźniki bólu u pacjentów nieprzytomnych, wentylowanych mechanicznie Non-verbal indicators of pain in unconscious, mechanically ventilated patients

14. Achterberg WP, Pieper MJ, van Dalen-Kok AH, de Waal MW, Husebo BS, Lautenbacher S, Kunz M, Scherder EJ, Corbett A. Pain management in patients with dementia. 2013:8:1471-82. doi: 10.2147/CIA.S36739. Epub 2013 Nov 1

15. Erdal A, Flo E, Aarsland D, Selbaek G, Ballard C, Slettebo DD, Husebo BS. Tolerability of buprenorphine transdermal system in nursing home patients with advanced dementia: a randomized, placebo-controlled trial (DEP.PAIN.DEM) 2018 May 16:13:935-946. doi: 10.2147/CIA.S161052. eCollection 2018

16. Chen K, Li H, Yang L, Jiang Y, Wang Q, Zhang J, He J. Comparative efficacy and safety of antidepressant therapy for the agitation of dementia: A systematic review and network meta-analysis 2023 Mar 3:15:1103039. doi: 10.3389/fnagi.2023.1103039

17. Lawn T, Aman Y, Rukavina K, Sideris-Lampretsas G, Howard M, Ballard C, Ray Chaudhuri K., Malcangio M. Pain in the neurodegenerating brain: insights into pharmacotherapy for Alzheimer disease and Parkinson disease 2020 Nov 24;162(4):999–1006. doi: 10.1097/j.pain.00000000000021

18. Liao YJ, Jao YL, Berish D, Hin AS, Wangi K, Kitko L, Mogle J, Boltz M. Systematic Review of Barriers and Facilitators of Pain Management in Persons with Dementia 2023 May;24(5):730-741. doi: 10.1016/j.jpain.2022.12.014. Epub 2023 Jan 9
19. Banks WA. Drug Delivery to the Brain in Alzheimer's Disease: Consideration of the Blood-brain Barrier 2012 May 15;64(7):629-39. doi: 10.1016/j.addr.2011.12.005. Epub 2011 Dec 17.

20. Wilco A, Lautenbacher S, Husebo B, Erdal A, Herr K. Pain in dementia *PAIN Reports* 5(1):p e803, January/February 2020. | *DOI:* 10.1097/PR9.0000000000000803(Eur J Pain 2020 Jan;24(1):192-208. doi: 10.1002/ejp.1477. Epub 2019 Oct 13.

21. Kunz M, Margot W.M de Waal, Wilco P. Achterberg, Gimenez-Llort L, Lobbezoo F, Sampson EL, van Dalen-Kok AH, Defrin R, Invitto S, Konstantinovic L, Oosterman J, Petrini L, van der Steen JT, Strand LI, de Tommaso M, Zwakhalen S, Husebo BS, Lautenbacher S. The Pain Assessment in Impaired Cognition scale (PAIC15): A multidisciplinary and international approach to develop and test a meta-tool for pain assessment in impaired cognition, especially dementia September 2019European journal of pain (London, England) 24(1) DOI:10.1002/ejp.1477

22. Defrin R, Beshara H, Benromano T, Hssien K, Pick CG, Kunz M. Pain Behavior of People with Intellectual and Developmental Disabilities Coded with the New PAIC-15 and Validation of Its Arabic Translation *Brain Sci.* 2021, *11*(10), 1254; https://doi.org/10.3390/brainsci11101254

23. Zwakhalen SM, Hamers JP, Abu-Saad HH, Berger MP. Pain in elderly people with severe dementia: A systematic review of behavioural pain assessment tools Published: 27 January 2006 BMC Geriatrics 2006, 6:3 doi:10.1186/1471-2318-6-3 Received: 26 July 2005 Accepted: 27 January 2006

24. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance Gillian https://doi.org/10.1016/j.sjpain.2016.06.012

25. Scherder EJ , Bouma A. Visual analogue scales for pain assessment in Alzheimer's disease Affiliations Expand PMID: 11111229 DOI: 10.1159/000022133

26. Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: a gender effect. PMID: 15943955. DOI: 10.1016/j.jpain.2005.01.351

27. Atee M, Hoti K, Parsons R, Hughes JD. Pain Assessment in Dementia: Evaluation of a Point-of-Care Technological Solution PMID: 28800333 PMCID: PMC5611807 DOI: 10.3233/JAD-170375

28. Zheng Q, Wang X. Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy. Protein & Cell, Volume 16, Issue 2, February 2025, Pages 83–120, https://doi.org/10.1093/procel/pwae026

29. Ando C, Hishinuma M. Development of the Japanese DOLOPLUS-2: a pain assessment scale for the elderly with Alzheimer's disease. Affiliations Expand PMID: 20860568 DOI: 10.1111/j.1479-8301.2010.00324.x