

Opioids in the elderly patients with cognitive impairment: A narrative review

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Abstract

Background: Assessment and management of pain in elderly people with cognitive impairment is particularly challenging. Physiological changes due to aging as well as comorbidities and polypharmacy are responsible for a complex clinical approach. Concomitantly, in cognitive impairment, including advanced dementia, changes in central nervous system along with changes in the peripheral nervous system due to aging have a significant impact in pain perception. Often clinicians decide to prescribe opioids in order to relief pain, also without a clear indication.

Aim: This review aims to investigate the effect of opioids in elderly patients with cognitive impairment.

Methods: A literature search of PubMed/Medline, Scopus, and Cochrane databases was conducted using keyword searches to generate lists of articles which were screened for relevance by title and abstract to give a final list of articles for full-text review.

Further articles were identified by snowballing from the reference lists of the full-text articles.

Results: This review discuss the complex physiological and pharmacological changes in elderly as well as the neurological changes that affect pain perception in this population. Additionally, it focuses on cognitive impairment and pain in Alzheimer's disease and other dementias, the pain assessment in the elderly with cognitive impairment as well as the safety of opioid use in elderly. Information regarding opioid prescription in nursing homes as well as recorded indications for opioids use, type and dosing of opioid and compliance of treatment in advanced dementia are also provided.

Conclusions: Opioid prescription in elderly population with cognitive impairment is particularly complex. All healthcare professionals involved in the care of such patients, need to be aware of the challenges and strive to ensure analgesic use is guided by appropriate and accurate pain assessment.

Keywords: aging; elderly; pain; opioids; dementia; cognitive impairment

Introduction

The world's population is ageing rapidly. Life expectancy has increased significantly in the last few decades. (Ramsay et al. 2020) In perspective, in Europe, the number of people older than 65 years will grow from 17.4% of the population in 2010 to 29.5% in 2060. In addition, there will be an increase in the percentage of people aged 80 years and older (the oldest-old), and by 2060 they will nearly have tripled to 12%. (Drenth-van Maanen, Wilting, and Jansen 2020) For the first time in history, most people worldwide can now expect to live into their 60s and beyond. (Drenth-van Maanen, Wilting, and Jansen 2020) A big concern is that ageing comes with an increase in disease burden and disability, including dementia.

Chronic pain is a major issue affecting more than 50% of the older population, in primary care (Camilloni 2021; Del Giorno et al. 2017). The situation is even worse in patients referred to pain clinics (Latina et al. 2019) and the prevalence is up to 80% of nursing homes residents. (Tinnirello, Mazzoleni, and Santi 2021) Pain treatment is increasingly recognized as an important clinical issue in people with cognitive impairment. (Cravello et al. 2017) (Cravello et al. 2019) There is a significant correlation between chronic pain and neurodegenerative processes, including cognitive decline. (Varrassi et al. 2015) The inability to verbalize the presence of pain leads to situations where pain might be neglected, under-reported, underestimated, misdiagnosed, and not adequately treated, imposing a strong impact on health and quality of life in this group of patients. (Achterberg et al. 2020)

Proper pain management is important for all, but especially for older adults with cognitive impairment (Paladini et al. 2015). This population is fragile and vulnerable to unrelieved pain due to a decreased ability to articulate pain and because some healthcare providers have erroneous beliefs regarding pain (Kaasalainen et al., 2007). However, the assessment of pain in advanced dementia is extremely challenging and complex, often resulting in under-treatment and poor pain management within the care home setting. (Schofield 2018)

To date there are only a few randomized clinical trials testing opioid therapy in elderly patients. The aim of this review is to investigate through a literature search strategy the efficacy and tolerability of opioid use in elderly people with cognitive impairment

Methods

In November 2021, we searched PubMed/Medline, Scopus, and Cochrane databases to identify relevant articles using a combination of the following search terms: “opioids”, “cognitive impairment”, “dementia”, “elderly”, “old”, “assessment” in various combinations. We used the Scale for the Assessment of Narrative Review Articles (SANRA) criteria. (Baethge, Goldbeck-Wood, and Mertens 2019) The primary search was supplemented with a secondary search using the bibliographies of the articles retrieved. Only full-length original articles were accepted.

We scanned 1392 articles for inclusion, and we narrowed our focus to studies including information about pain in the elderly with cognitive impairment or dementia, pain assessment, opioid use in this group, safety, and tolerability as well as cognitive impact and neurological alterations. All retrieved articles were initially reviewed for inclusion by title and abstract by two authors (MR, GV). We included articles referring to pain (acute or chronic) in adults with dementia or cognitive impairment and opioids to have been used. This narrative review article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. Hence, it does not need any approval by Ethics Committees.

Physiological Changes in Elderly

Neurological Changes affecting pain perception in the Elderly

Oxidative stress, chronic inflammation, changes in energy metabolism and mitochondrial dysfunction in stress response contribute to neurodegeneration in older adults (Rekatsina et al. 2020) and cognitive decline.(Chippa and Roy 2021) Elderly subjects appear to be more susceptible to prolonged pain development; medications acting on peripheral sensitization are less efficient. (Chippa and Roy 2021)

Pathologic changes in the central nervous system are responsible for different pain processing and response to treatment. (Tinnirello, Mazzoleni, and Santi 2021) Areas of the brain involved in pain perception and analgesia are susceptible to pathological changes such as gliosis and neuronal death and the effectiveness of descending pain inhibitory mechanisms, particularly their endogenous opioid component, also appears to deteriorate with advancing age. (Tinnirello, Mazzoleni, and Santi 2021) Hyperalgesia is more common at older age and recovery from peripheral nerve injury appears to be delayed. (Tinnirello, Mazzoleni, and Santi 2021) In addition, peripheral nociceptors may contribute minimally to pain sensation at either acute or chronic time points in aged populations. (Tinnirello, Mazzoleni, and Santi 2021) The density of unmyelinated fibers in the peripheral nervous system decreases considerably and leads to slowing of nerve conduction, changing the pain perception (Verdú et al. 2000). There is loss of brain volume in prefrontal cortex and hippocampus, essential centers for pain perception, as part of normal ageing. (Rodriguez-Raecke et al. 2009) The above changes are likely to interact with brain alterations that appear to be caused by persistent pain, such as reduction in volume of thalamus associated with pain duration, (Rodriguez-Raecke et al. 2009) and decreased functioning of endogenous pain modulatory mechanisms. (Cole et al. 2010)

Age related changes in pharmacokinetics

The ageing process is characterized by structural and functional changes affecting all organ systems and results in reduced homeostatic capacity. (Mangoni and Jackson 2004) Although

the function of a particular system may be maintained during resting conditions, the reduction of functional reserve is responsible for an increased vulnerability to stress. (Mangoni and Jackson 2004) The reduced homeostatic ability affects different regulatory systems in different subjects, thus explaining at least partly the increased interindividual variability occurring as people get older. (Mangoni and Jackson 2004)

The absorption, distribution, metabolism, and excretion of drugs are affected to a varying extent by the ageing process itself and by diseases commonly associated with ageing. (Drenth-van Maanen, Wilting, and Jansen 2020) There is a reduction in gastric acid production, drug bioavailability, small bowel surface, splanchnic blood flow as well as a reduced first-pass metabolism, all of which affect absorption (Drenth-van Maanen, Wilting, and Jansen 2020). The distribution of the drugs is affected by the increased proportion of body fat as well as the decreased total body water, the decreased lean body mass, and the increased α -I-acid glycoprotein levels. Malnutrition and proteinuria lead to hypoalbuminemia which also has a role in drug distribution (Drenth-van Maanen, Wilting, and Jansen 2020). Liver diseases or normal physiological effects of ageing on the liver as well as polypharmacy can affect metabolism. (Drenth-van Maanen, Wilting, and Jansen 2020) Finally the elimination of drugs is affected by decreased renal function and renal disease. (Drenth-van Maanen, Wilting, and Jansen 2020) All these changes lead to a prolongation of plasma elimination half-life (Mangoni and Jackson 2004) and an increased risk of adverse reactions to water-soluble drugs (Gianni et al. 2009)

Opioid related pharmacokinetics in the elderly

It is important to highlight the differences of the most used opioids in terms of their pharmacokinetics, and hepatic and renal impairment. Morphine is metabolized in the liver to an inactive metabolite morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which is a potent analgesic. Both metabolites are eliminated by the kidneys and secreted through the urine leading to metabolite accumulation in renal impairment, and possible intoxication. (Glare and Walsh 1991) Oxycodone has many active metabolites that may accumulate during renal dysfunction. (Gianni et al. 2009) Hydromorphone has only one glucuronide, which is neuroexcitatory and accumulates during renal dysfunction. (Gianni et al. 2009) Fentanyl is metabolized by the liver into the active norfentanyl along with several other unspecified inactive metabolites. (Gianni et al. 2009) Nearly 10% of the active substance is not metabolized, with less than 10% of the inactive metabolite, norfentanyl, eliminated by the biliary system and excreted in the faeces. Approximately 75% of metabolites are eliminated in the urine. Therefore, during renal impairment, the clearance of fentanyl is reduced, and its half-life is prolonged. Buprenorphine is partially (only 30%) metabolized by the liver into three major metabolites: norbuprenorphine, buprenorphine-3-glucuronide and norbuprenorphine glucuronide. (Gianni et al. 2009) (Pergolizzi and Raffa 2019) (Pergolizzi et al. 2019) Approximately two-thirds of the parent drug are eliminated by the biliary system in the faeces. The metabolites are eliminated mainly by the biliary system and in a small quantity of buprenorphine by the renal system. Even though the half-life of the

drug is prolonged during hepatic impairment, the low activity of the metabolites does not cause significant clinical relevance. However, careful monitoring of patients with hepatic impairment is recommended. During renal impairment, there is no clinically important accumulation of metabolites, thus dose reduction is not necessary. (Gianni et al. 2009)

Definition of cognitive impairment and dementia

Cognitive impairment in the elderly is a common condition. Mild cognitive impairment is defined as cognitive decline more than expected for an individual's age and level of education, but interfering notably with daily life activities. On the other hand, dementia is more severe and widespread with a significant effect on daily function. (Chippa and Roy 2021) In persons over 70 years, 14% have sufficient cognitive impairment to warrant a diagnosis of dementia (Plassman et al. 2007) and an equal number have milder clinical image but unequivocal cognitive impairment (Petersen et al. 2010)

Cognitive impairment and pain in Alzheimer's disease (AD) and other dementias

The neurodegeneration that occurs in AD affects important areas involved in the medial pathway of pain, the medial nuclei of the thalamus, hypothalamus, cingulus and insula, whereas the brain areas involved in the lateral pathway of pain are relatively well preserved. (Braak and Braak 1997) This is important as the typical neurodegeneration of AD involves the affective-motivational component of pain (medial pathway) rather than the sensory-discriminative dimension. (Scherder and Bouma 1997) The perception of acute pain is preserved while the experience of chronic pain may be altered, (Pickering, Jourdan, and Dubray 2006) whereas a reduction in the autonomic response as a result of impending pain has also been reported. (Benedetti et al. 2004)

The prefrontal lobe is also affected by neurodegeneration in AD, leading to altered response to analgesics. This effect is particularly noticeable when the connections between the prefrontal lobes and the rest of the brain are extensively damaged. (Benedetti et al. 2006) Significantly, although It remains unconfirmed, those patients might require higher dosages of analgesics. Additionally, it is still unclear whether the changes in the blood–brain barrier that occur during the dementia influence the effect of centrally acting pain medications, such as opioids. (Banks 2012)

In vascular dementia (VaD), pain perception may increase because of white matter lesions of pathways ascending to the thalamus, such as the spinothalamic tract. (Jellinger 2008) Only a few studies reporting on chronic pain in patients with VaD observe that the level of pain reported by patients with VaD is significantly higher than that reported by patients without dementia (Scherder et al. 2003) (Scherder et al. 2015) (van Kooten et al. 2017)

Patients with mild to moderate AD and mixed AD and VaD are less likely to report pain than patients with subjective cognitive impairment in an outpatient clinic setting (Binnekade et al. 2018)

Assessment of pain in the Elderly with cognitive impairment

Pain in cognitive impairment and dementia is poorly or inaccurately diagnosed due to patient's unwillingness to complain, atypical pain presentations, multiple co-morbidities, and cognitive decline. (de Tommaso et al. 2016) The need of time to consider the question, difficulty in hearing and understanding, memory deficit, acute confusion (delirium) may hinder the assessment. (Hale and Marshall 2017) Self-assessment scales are considered the "gold standard" for pain assessment, but the presence of cognitive impairment is likely to reduce the reliability of these measures.(Cravello et al. 2019)

A recent survey across Europe on current practices, use of assessment tools, guidelines, and policies for pain in older adults with dementia identified 17 pain assessment scales (including different versions of scales) to be used worldwide in care home settings for those with advanced dementia. (Felton et al. 2021) The most frequently used tools are PACSLAC (Pain Assessment Checklist for Seniors with Limited Ability to Communicate - including three variations (Fuchs-Lacelle and Hadjistavropoulos 2004)) and PAINAD (Pain Assessment in Advanced Dementia) (Warden, Hurley, and Volicer 2003) (Felton et al. 2021). The choice of these tools recognizes them as international scales with good psychometric qualities and clinical utility, developed by experienced dementia care clinicians, and are specific for this population of patients. MOBID (Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale) (Husebo et al. 2007) and MOBID2 were also developed for this population with some established validity. (Felton et al. 2021) The Abbey Pain Scale was only used in less studies, which may reflect its lack of validity and internal reliability. However, it is used widely in the UK and Australia as a useful, easy to use clinical device and is recommended by the Australian Pain Society. (Felton et al. 2021)

A survey in seven European countries has highlighted that the range of tools being used varied across countries and while participants generally reported that these pain assessment tools were easy/very easy to use, they were difficult to interpret. (Zwakhlen et al. 2018) While many of these tools rely on facial expression of pain, facial expressions were the least useful in comparison to other items. Furthermore, findings showed that nurses employed in long-term care settings did not feel that they were educated enough in pain assessment and management.

Other tools such as Disability Distress Scale (DisDat), Pade, Universal Pain Assessment Tool (Paine), Doloplus, NoPain, Pain Assessment Scale for Seniors with Severe Dementia (Pacslac), Checklist of Nonverbal pain indicators (CNPI), Assessment of discomfort in Dementia (ADD), Bolton Pain Assessment Tool (BPAT), Numerical Rating Scale (NRS), Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), NRS, Faces Rating Scale (FRS) have also been reported for assessment of pain in advanced dementia.(Schofield 2018)

It is important to recognize that pain tools are problematic in dementia due to various reasons. Although many tools have been developed to assess pain for people with cognitive impairment, they have major drawbacks in people with moderate to severe communication difficulties, since there is no evidence that pain generates unique signs and behaviors. This alone should preclude the use of pain tools in patients with poor communication. Also, people with communication difficulties seem to have unique patterns of distress signs and behaviors that are the same regardless of the cause (e.g. for fear, frustration, and anger), but will prompt the use of an analgesic. (Regnard 2021)

Safety of Opioid Use in Elderly

The tolerability of opioids is extremely important in older people compared to their younger peers, because adverse events such as drowsiness, dizziness and motor imbalance have more serious consequences in older frail patients already at a greater risk of falls. (Gianni et al. 2009) Indeed a recent study supported that there is an increased risk of hip fracture in elderly with Alzheimer when using opioids. (Taipale et al. 2019) The risk was low with weak opioids, mean with buprenorphine and high with the use of strong opioids. In older patients the increased gastric pH, the reduced gastric and intestinal motility, as well as the decreased enzyme activity and absorption lead to prolonged colon transit times, constipation and gastrointestinal disturbances. (Gianni et al. 2009) Opioids' neurological side effects as sedation, confusion, hallucinations, and loss of cognition is an important issue in the elderly. Most opioids have the risk of such effects especially at high doses for long periods of time and/or when patients present with severe renal failure. (Gianni et al. 2009)

Low-dose transdermal buprenorphine and a low dose of oxycodone administered by mouth showed lack of Central Nervous System (CNS) complications. (Gianni et al. 2010) Moreover, buprenorphine and transdermal fentanyl produce less constipation than morphine and oxycodone, and may be preferable to other opioids when constipation cannot be easily managed. (Rekatsina et al. 2021)

In elderly patients with impaired hepatic and renal function, the accumulation of metabolites from specific opioids, such as morphine, is important to recognize. In patients with renal dysfunction as well as in the elderly the half-life of the active drug and metabolites is increased for all opioids except buprenorphine, therefore doses should be reduced, a longer time interval should be used between them, and creatinine clearance should be monitored. (Dolati et al. 2020; Vadivelu and Hines 2008)

Another adverse effect of high dose opioids may be the respiratory depression, with elderly patients being more vulnerable. This effect is mediated by the μ -opioid receptor, where agonists such as morphine and fentanyl with clear dose-dependent effect are very susceptible. (Dahan et al. 2005) Morphine, oxycodone, hydromorphone, fentanyl, and methadone cause a dose dependent decrease in respiration, with apnea at high doses. Buprenorphine has a well-defined ceiling effect for respiratory depression due to an intrinsic analgesic activity of the

receptor (Walsh et al. 1994) and can be reversed with opioid antagonists, such as naloxone. (Dahan et al. 2005)

It is also important to highlight the effects of opioids on the immune system as they lead to a gradual immunosuppression (Franceschi et al. 2000). Morphine is the most immunosuppressive among them. (Mellon and Bayer 1998)

Drug interactions and protein binding represent additional important safety issues. Some opioids are metabolized by CYP P450 isoenzymes with a variability that is largely determined by genetic polymorphisms, which may account for high rates of side-effects or minor efficacy in affected patients. This applies to oxycodone and tramadol, which are metabolized by CYP 2D6, and to buprenorphine, which is metabolized by CYP 3A4. (Iribarne et al. 1998; Iribarne et al. 1997) Regarding protein binding, buprenorphine seems to be the safest choice for older adults as it binds to alpha and beta globulins, unlike most drugs, which bind to albumin, minimizing the likelihood of drug–drug interactions related to protein binding for this drug. (Umehara, Shimokawa, and Miyamoto 2002) (Zhang et al. 2003)

Pneumonia was also associated with opioid use in elderly with Alzheimer’s Disease. The highest risk was observed during the first two months of use. Compared to weak opioids, buprenorphine was not associated with a higher risk, whereas strong opioids were. The risk was higher for those using ≥ 50 morphine milligram equivalents (MME)/day compared to using < 50 MME/day. (Hamina et al. 2019) Risk-minimization strategies should be considered if opioid therapy is needed.

A study investigating the association among the use of opioids and dementia related neuropathology did not show greater neuropathologic changes with greater exposure, as it did with NSAIDs (Dublin et al. 2017)

Pharmacological treatment should consider physiological changes, high comorbidity and drug interactions that occur very frequently in the elderly. (Tinnirello, Mazzoleni, and Santi 2021)

Opioid prescription in nursing homes

Among studies investigating the use of opioids in elderly patients with cognitive impairment, there is a great variation in prevalence. In a cross-sectional study conducted in the USA, of all long-stay residents, one in three were prescribed any opioid, and one in seven were prescribed opioids long-term. (Hunnicutt et al. 2018) Cognitive impairment was associated with less frequent opioid use after adjusting for pain-related diseases, disabilities, and depressive symptoms. However, the association was not explained by the estimated severity of pain, (Mörttinen-Vallius, Hartikainen, Huhtala, et al. 2021) suggesting that the pain of home care clients with cognitive impairment may not be treated optimally. (Mörttinen-Vallius, Hartikainen, Huhtala, et al. 2021) Another recent observational study identified that home care residents with and without dementia use opioids for long periods of time for pain, mostly for non-malignant musculoskeletal disorders: vertebral osteoporotic fractures (21.6%),

degenerative spinal disorders (20.9%), and osteoarthritis (20.6%)). (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021) The prevalence of daily opioid use was 9.3% and the duration more than twelve months. (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021) Interestingly, according to another study the prevalence of opioid use in 2000-2015 resulted increased by 35% among elderly with dementia and only by 13% among elderly without. (Jensen-Dahm et al. 2020) Similar studies also suggest that opioid use in elderly with dementia was frequent and almost twice as high compared to elderly without dementia (32.5% in elderly with dementia and 16.9% in those without). (Jensen-Dahm et al. 2019)

It is alerting that in nursing home residents with advanced dementia, despite the relatively prevalent use of strong prescription opioids, pain was still prevalent in two out of three patients. (Griffioen et al. 2019) In the same study, on resident with advanced dementia 19.3% were prescribed opioids, and of these 79.4% were still in pain. (Griffioen et al. 2019)

A cross-sectional chart audit from the USA on verbally communicative nursing home residents concluded that residents without a dementia diagnosis were significantly more likely to have a medication order for an opioid. (Monroe et al. 2014) Notably, 40% of nursing home residents with dementia who died from cancer did not receive any opioid during their presence in the residential structure. Severely cognitive impaired nursing home residents requiring opioids are at great risk of suffering from untreated advanced cancer pain. (Monroe et al. 2013)

Several studies from Northern Europe suggest that a great amount of nursing home (NH) residents with advanced dementia receive strong opioids, 19.3% in Norway in 2019 (Griffioen et al. 2019) 17.9% in Norway in 2011 (Sandvik et al. 2016), 27.8% in Denmark in 2010 (Jensen-Dahm et al. 2015), and 13.5% in Finland in 2011. (Pitkala et al. 2015) In a study conducted in NH resident in Norway, despite prevalent prescription of strong opioids (almost 20%), the dosage was relatively low on average but almost 80% of the NH residents with prescribed strong opioids still showed signs of pain. (Griffioen et al. 2019)

Among community-dwelling persons with Alzheimer Disease (AD), overall long-term opioid use was more common among persons without AD (8.7%) than among persons with AD (7.2%, $P < 0.0001$). However, among opioid users, prevalence of long-term opioid use was slightly higher among patients with AD than among those without AD (34.2% vs 32.3%, respectively, $P = 0.0004$). Long-term use of transdermal opioids was more than 2-fold among opioid users with AD (13.2%) compared with users without AD (5.5%). Factors associated with long-term opioid use included AD, age ≥ 80 years, female sex, rheumatoid arthritis, osteoporosis, low socioeconomic position, history of substance abuse, and long-term benzodiazepine use. Prevalence of long-term opioid use was somewhat similar among both groups. (Hamina et al. 2017)

Recorded indications for opioids use in advanced dementia

Opioids are used for cancer and non-cancer, acute or chronic pain in older people with advanced dementia. A recent observational study revealed the indications where opioids had been prescribed. (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021) Non-malignant diseases comprised most indications for opioid use. Only 3.2% of the study population used an opioid for cancer-related pain. Musculoskeletal disorders were the indication for opioid use for over four-fifths of the study population and the most common were vertebral osteoporotic fractures, degenerative spinal disorders, and osteoarthritis (21.6%, 20.9%, and 20.6%, respectively). Other acute fractures or fall-related injuries, muscular pain, and tendinopathy and arthritis were minor reasons within this group. Interestingly, neuropathic pain was the indication for opioid use for 13.1% of the study population, and other rare indications were cardiovascular diseases, surgery, other neurologic diseases, psychiatric conditions, gastrointestinal symptoms, and decubitus ulcers (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021) (Gianni et al. 2009)

Adherence/compliance to treatment

Estimates of the extent of non-adherence in the elderly vary from 40% to 75% and can be either overdose or underuse. Older patients might take more than the prescribed dose in the misbelief that this will have a greater beneficial effect. Skipping a dose is particularly common when there is cognitive decline, or in patients receiving polypharmacy. Under-use is most frequent; inappropriate drug discontinuation may occur in up to 40% of patients, particularly within the first year of a chronic care regimen. (Salzman 1995) Various strategies can be used to improve adherence in elderly patients. Communication between physician and patient should be optimized as far as possible to enable educational interventions and caregivers involving and patient's family support. (DiMatteo 2004)

Opioid type and dosing

Codeine and tramadol, considered weak opioid, were used by 22.3% of the study population, while buprenorphine by 61.7%, and strong opioids (fentanyl, morphine, or oxycodone) by 18.1%. Buprenorphine was the most commonly used opioid (61.7%; median dose 10 µg/h, range 5-20 µg/h), followed by codeine (combined with paracetamol; 15.2%; median daily dose 79 mg, range 30–180 mg), oxycodone (14.2%; median daily dose 17.5 mg, range 5–120 mg), tramadol (7.1%; median daily dose 100 mg, range 50–300 mg), transdermal fentanyl (2.1%; median dose 18.5 µg/h, range 12–75 µg/h), and morphine (1.8%; median daily dose 10 mg, range 8–20 mg). None of the study population used hydromorphone. (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021) During the follow-up period, approximately one out of three patients switched from one opioid to another. Among the opioid users with dementia, buprenorphine was the more commonly used (Mörttinen-Vallius, Hartikainen, Seinelä, et al. 2021)

However, the declining organ function and other physiological changes in elderly require lower initial doses of analgesics and less frequent dosing intervals. **(Schuler and Griebinger**

2015)The therapeutic options for non-cancer pain are increasing and there are now several oral sustained release and patch preparations. The desired advantage of sustained release or steady state administration compared with intermittent dosing of an opioid (or any drug) is maintaining a steady plasma level of the drug within a therapeutic range to avoid peaks, excess adverse effects or inadequate pain relief, however adequate compliance is required. (Gianni et al. 2009)

According to literature, 66.7% of opioid prescriptions of NH residents with advanced dementia were less than or equal to the lowest dosage of fentanyl patches (12 mcg/h) or buprenorphine (5 or 10 mcg/h). (Griffioen et al. 2019) In another study, buprenorphine and fentanyl (primarily patches) were commonly used among NH residents (18.7%) and home-living patients with dementia (10.7%) but less often by home-living patients without dementia (2.4%).(Jensen-Dahm et al. 2015) Among persons with Alzheimer's Disease, long-term opioid use was strongly associated with transdermal opioids. (Hamina et al. 2017)

A randomized, placebo-controlled trial (DEP.PAIN.DEM) regarding tolerability of buprenorphine transdermal system in NH patients with advanced dementia showed that active buprenorphine 5 µg/hour had significantly higher risk of discontinuation compared with placebo in people with advanced dementia and depression, mainly due to psychiatric and neurological adverse events. Daytime activity dropped significantly during the first week of treatment. Concomitant use of antidepressants further reduced the tolerability of buprenorphine. (Erdal et al. 2018)

A prospective, observational pilot study with low-dose oral prolonged-release oxycodone/naloxone for chronic severe pain in elderly patients with cognitive impairment and substantial impairment in daily functioning showed that the above combination was effective in improving pain and other symptoms associated with dementia, with a favorable safety and tolerability profile and did not worsen bowel function. Substantial improvements in daily functioning and neuropsychiatric symptoms were also reported. (Petrò et al. 2016)

A study on efficacy and tolerability of tapentadol extended release for the treatment of non-malignant chronic low back pain in elderly patients concluded that when this drug is titrated to the optimal dose it maintains efficacy and good tolerability. It achieved a 50% pain relief in 58% of elderly patients and improved quality of life and sleep whereas the performances in global cognition and sustained attention tasks remained stable or improved. However, it is important that 25% of the study population discontinued the treatment due to side effects during titration. (Freo et al. 2021) Before this study, "TaPE study" with a focus on anxiety, depression, cognitive status, and life quality prolonged release had also confirmed that low doses of tapentadol in the long-term management of chronic musculoskeletal pain in the elderly, adequately titrated according to patients' response, are safe and effective. A limited number of minor adverse effects was noted only at the beginning of treatment, and with goal-directed and adequate patients' information therapy adherence remained high throughout the study period. (Tarsitano et al. 2019) In a retrospective analysis, tapentadol was effective on pain and well tolerated in Parkinson Disease patients. During treatment cognitive, and motor

functions were unchanged or improved. Mood level and quality of life also improved. The study however did not focus on Parkinson's Disease dementia patients. (Freo, Furnari, and Ori 2018)

Limitations

This is not an exhaustive review of the current evidence. However, it provides the clinician with an insight of the pain perception in the elderly population with cognitive impairment, along with significant information regarding pain assessment and evidence regarding current opioid prescription practice.

Conclusions

This review focuses on eradicating the misconception among some healthcare professionals that elderly people, especially those affected by cognitive decline, have a reduced perception of pain. Standardized instruments can improve physician/patient communication and understanding of the patient's pain experience, while physiological changes must be considered when prescribing drugs for elderly patients. Additionally, specific changes that appear in dementia patients should be considered when assessing and treating pain. When prescribing opioids, the gold standard is to start at a low dose and cautiously titrating due to polypharmacy and concomitant diseases. Specific guidelines focusing on specific pathophysiological changes in the elderly with cognitive impairment are needed to ensure adequate treatment of chronic pain conditions and ensure personalized and focused pain management.

Acknowledgment

The views expressed are those of the authors, and not necessarily coincide with those of the NHS of any of the countries of the authors.

Compliance with Ethics Guidelines. This article is based on previously published studies and does not contain any original data derived from studies on humans or animals performed by the authors.

Funding. This research was funded in part by the Paolo Procacci Foundation.

Editorial Assistance. The authors acknowledge editorial services by Jo Ann LeQuang.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Martina Rekatsina carried out most of the selection of the articles and drafted the initial manuscript. All the authors contributed to review and to critically improve the quality of the paper.

Disclosures. Giustino Varrassi is a member of the journal's Editorial Board. The other authors have nothing to disclose

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