Romayne Gallagher, MD, CCFP, FCFP

Opioids for pain and shortness of breath in frail older adults: How to choose and use

Early opioid intervention in older adults with persistent disabling pain that does not respond to acetaminophen or other interventions may prevent increasing frailty and loss of independence.

ABSTRACT: Opioids are indicated for persistent moderate to severe pain that impairs function and quality of life. Two case examples are used to present a review of the pharmacokinetics and pharmacogenomics and provide practical and evidence-based information required to safely treat pain in older adults. In those with significant cognitive impairment, pain is not verbalized but may be tracked through neuropsychiatric symptoms and behavior. The approach to diagnosis and treatment is based on resident, family, and staff subjective and objective criteria tracked over time as analgesics, including opioids, are titrated.

Opioids are indicated for the management of persistent moderate to severe pain that is severe enough to impact function and quality of life[1] and is not alleviated by non-opioid therapies. Chronic pain is common in older adults and is associated with frailty and loss of function.[2] Early identification and successful management of chronic pain is essential and may prevent loss of independence. Opioids are also indicated for disabling dyspnea that is unresponsive to usual therapies in advanced disease of any cause.

This article focuses on how to prescribe safely and effectively in frail older adults. Safety involves the individual patient, the prescribing physician, and the community. This article assumes that each patient who was started on opioids had a pain diagnosis, a mental and psychological assessment, and a determination of their opioid use disorder risk using the Screener and Opioid Assessment for Patients with Pain - Revised or opioid risk tool. The Brief Pain Inventory (www.npcrc.org/files/news/briefpain_short.pdf) is best for measuring pain-related effect on function, mood, and sleep, and repeated testing can establish if progress is occurring. In those patients who are capable, goals should be developed with them regarding using opioids to help them increase function, exercise tolerance, and socialization. The College of Physicians and Surgeons of BC practice standard (www.cpsbc.ca/files/pdf/PSG-Safe-Prescribing.pdf) should be consulted and universal precautions should be used for opioid prescribing. A list of common opioids and relevant pharmacokinetics is provided in the **Table**.[3-6]

Case data

Patient A, mild frailty but losing function quickly

Patient A, who is 82 years old, has lumbar spinal stenosis and right-sided L5 nerve root compression. Other comorbidities include hypertension, osteoarthritis, macular degeneration, asthma, and a history of cancer. Epidural steroid injections were effective for pain management for 6 years, but now they do little to relieve her pain. Gabapentin and pregabalin were both trialed; they did little for pain and caused fluid retention and drowsiness. She rates her pain as 5–8/10, and it is maximal when she is standing or walking. Her poor vision had reduced her function, but now her world is contracting significantly due to reduced mobility, and she requires help with all instrumental activities of daily living.

A trial of opioids is appropriate since she has not responded to non-opioids and other therapies and is losing function, but to select an opioid, three things must be reviewed: age, renal function, and previous opioid experience.

Age. Older adults display a greater sensitivity to CNS-active medications[7] and generally require a lower dose than younger adults to control their pain. Older adults are more sensitive to serum-level changes with short-acting opioids and experience fewer side effects with long-acting formulations. Some long-acting opioids come in a dose that is low enough

Dr Gallagher is a clinically retired member of the Department of Family and Community Medicine (Honorary Staff), Providence Health Care, Vancouver, and a clinical professor in the Faculty of Medicine, Division of Palliative Care, University of British Columbia.

This article has been peer reviewed.

to be initiated in those already taking several short-acting doses as needed per day, and a buprenorphine patch is safe for use in opioid-naive patients.

Renal function. Renal function is important because almost all opioids are excreted through the kidneys. Only methadone and buprenorphine have significant excretion through the bowel, but this makes them well tolerated in people on dialysis or with significant renal failure.[8,9] Patient A's renal function is near normal at an estimated glomerular filtration rate of 57. While it is normal for her age, it has diminished.

Previous opioid experience. Having details of previous opioid use, its efficacy, and adverse effects helps eliminate opioids that are not well suited to Patient A's pharmacogenomics. Up to 25% of people have polymorphisms in the genes that control opioid pharmacokinetics and pharmacodynamics.[10] Patient A notes that she has been given Tylenol #3 before with no effect, and it makes her nauseated. Likely, she is a poor metabolizer and the codeine is not being metabolized by the CYP2D6 enzyme to its active molecule—morphine—resulting in poor analgesia and side effects. Ultrarapid metabolizers are also at risk because they metabolize much more of the codeine into morphine,

TABLE. Common opioids and relevant pharmacokinetics.[3-6]

Name	Chemical structure	Activity*	Opioid receptor binding affinity	Half-life (hours)	Metabolism	Active metabolites	Excretion	Drug distribution	Miscellaneous
Codeine	4,5-epoxy-morphinan ring	Prodrug CYP2D6	μ+	3–5	Glucuronidation of morphine	+++	Renal	Hydrophilic	Weak opioid; morphine is the active analgesic
Morphine	4,5-epoxy-morphinan ring	+	μ+++ κ+	3–5	Glucuronidation	+++	Renal	Hydrophilic	Higher risk of neurotoxicity
Hydromorphone	4,5-epoxy-morphinan ring	+	μ+++	2–4	Glucuronidation	++	Renal	Hydrophilic	Better tolerated in older adults than morphine
Oxycodone	4,5-epoxy-morphinan ring	+	μ+ κ++	3–5	CYP3A4	0	Renal	Hydrophilic	Available in very small long-acting doses
Fentanyl	phenyl-piperidines	+	μ+++	21–30	CYP3A4	0	Renal	Lipophilic	Large fat storage; onset of effect delayed
Methadone	diphenyl-heptylamines	+	μ+++ NMDA	24 or longer	CYP3A4 CYP2B6	0	Gut	Lipophilic	The Methadone4Pain course should be completed before prescribing: www.methadone4pain.ca
Buprenorphine transdermal	4,5-epoxy-morphinan ring	+	μ+++ κ+ δ+	13–35	CYP3A4	0	Gut	Lipophilic	Large first-pass liver effects; poor oral availability; patch well tolerated in elders
Tramadol	Atypical	Prodrug CYP2D6	μ+ Noradrenalin/serotonin	9	CYP3A4	+	Renal	Hydrophilic	Weak opioid; side effects/drug interactions from serotonin reuptake inhibition
Tapentadol	Atypical	+	μ+++ Noradrenalin	4.5	Glucuronidation	0	Renal	Hydrophilic	May be useful if other strong opioids are not effective

Note: The opioids in the table are arranged in categories according to their structure, metabolism, and receptor target. When switching an opioid due to inadequate analgesia or intolerable side effects, switch to a different opioid category to achieve a better result.

* Prodrug/weak opioids require an enzyme to become analgesic. They have an analgesic ceiling dose.

δ = delta opioid receptor

κ = kappa opioid receptor

μ = mu opioid receptor

CYP2B6 = cytochrome P450 2B6

CYP2D6 = cytochrome P450 2D6

CYP3A4 = cytochrome P450 3A4

NMDA = n-methyl-d-aspartate

which results in toxicity, particularly when pregnant or breastfeeding. Oceania and Middle Eastern ethnicities have the highest rate of ultrarapid metabolism at 21%, and Europeans and people of Jewish lineage have the highest rate of poor metabolism, near 6%.[11] Because of polymorphisms and their potential danger, Health Canada does not recommend codeine use in those under 18 years of age or in pregnant or breastfeeding women. All prescriptions for codeine alone now require a duplicate prescription. Because of codeine's issues (poor analgesia, dose ceiling, side effect profile, addiction-related harm), there have been calls to delist it.[12]

Codeine and tramadol need CYP2D6 to metabolize them into analgesics, and therefore, have a ceiling dose limited by enzyme conversion. For this reason, they are called *weak opioids*. The National Opioid Use Guideline Group recommends them as first-line only because of their lower abuse potential, but they are not good choices in older adults. Tramadol, with its serotonin-reuptake inhibition action, has significant drug interactions in addition to the genomics effect on activation.[13]

Patient A says "morphine made her crazy" after her surgery for her breast cancer, and she found it very frightening. It is probably best to avoid morphine and codeine and be cautious with hydromorphone—morphine's sister. If the patient is fearful of trying it again, even if it is something that could be managed (nausea in the first week), listen to the patient and choose something else.

Cognitive effects

Opioid-induced neurotoxicity is a continuum of adverse effects ranging from impaired concentration to impaired executive function and psychomotor effects, and hallucinations, delirium, and seizures.[14] Sedation is another effect that can range from being mild and transient when starting or increasing the dose, through to a decreasing level of consciousness preceding ventilatory difficulties and apnea. Severe cognitive effects such as delirium are more common in older adults or those with fragile central nervous systems due to comorbidities.[15] However, opioid metabolites from codeine, morphine, and hydromorphone are known to be neurotoxic and accumulate in older adults and those with renal failure, resulting in opioid-induced neurotoxicity.[16] While any opioid can cause some degree of neurotoxicity, it is wise to avoid these opioids in patients with renal failure, fragile central nervous systems, or previous cognitive effects. Many mild symptoms of opioid-induced neurotoxicity, such as impaired attention, misperceptions, and bad dreams, are often not reported by patients unless asked. Rotating to a different opioid can resolve this.

Opioids are indicated for the management of persistent moderate to severe pain that is severe enough to impact function and quality of life.

Opioids are not all the same

In a 2016 study,[17] 520 people with cancer pain that was being treated with opioids were randomly selected to receive either morphine, oxycodone, buprenorphine, or fentanyl for 1 month. The average age of the participants was 67 years, 80% had other morbidities, and their Karnofsky performance scale indicated mild frailty.[18] They were observed for analgesic efficacy and adverse reactions. Approximately 25% of patients were poor to non-responders and had to be switched to another opioid or have adjuvant medications added. The number of discontinuations/switches from morphine were significantly higher than for the other opioids, and the number of dosage adjustments for fentanyl were also significantly greater. Adverse events were not significantly different among the four opioids except for the significant neurotoxicity of morphine. This study supports the observed interindividual variations in opioids (approximately 25% of participants needed rotation or addition of adjuvants, no matter which opioid they were on) and required ongoing adjustment to maintain analgesia. It confirms that morphine is not the drug of first choice in older adults, and even more so in frail older adults.

Opioids of first choice in frail older adults

The opioids of first choice in older adults and those with renal failure are fentanyl, methadone, and the buprenorphine patch.[19] Oxycodone has clinically insignificant metabolites[20] and is often well tolerated in older adults. Hydromorphone is better tolerated than morphine because it has a shorter half-life,[21] but in severe renal failure, it should be avoided. The opioids of last choice are morphine and codeine. Tramadol requires activation like codeine, and its adverse safety events (falls/fractures and emergency visits) are equal to those associated with strong opioids.[22] As always, the choice will be a compromise between what is best, what is available, and what is affordable.

Before starting Patient A on a low-dose regular opioid, she should be advised of the side effects and how they will be managed. Constipation is ubiquitous in older adults, so it should be prevented by starting polyethylene glycol 3550 with the opioid. If constipation is severe, consideration should be given to using fentanyl or buprenorphine because they are transdermal, or to using the oxycodone/naloxone combination product. Because Patient A had nausea with previous opioids, she should be prescribed regular metoclopramide for the first week when nausea is most prominent and then be allowed to wean herself off as tolerated.

Finally, Patient A should be told that she may experience some sedation in the first few days and should be warned about doing anything that requires strict attention (e.g., driving, looking after grandchildren). This sedation should completely clear by 1 week, but if not, an opioid switch may be warranted.

Respiratory depression

The rare side effect that makes physicians reluctant to use opioids is respiratory depression. Respiratory arrest is the cause of death from illicitly made fentanyl that poisons the illicit supply of heroin and other psychoactive drugs. Almost all the people who have suffered this tragic outcome have multiple CNS depressants in their system, such as alcohol, benzodiazepines, antidepressants, neuroleptics, and other illicit opioids, as well as an unknown massive quantity of fentanyl or a derivative.

Physicians should ensure that they rationalize the use of CNS depressants when prescribing opioids. Benzodiazepines are not recommended in adults over 65 years of age.[23]

Opioids suppress both the rhythm of breathing and the hypoxic and hypercapnic ventilatory response—brainstem control centres that monitor and respond to changes in oxygen and carbon dioxide.[24] Naturally, suppression is worse with a rapid IV infusion of high-dose opioids with other CNS depressants already in the patient's system.

Pain stimulates the respiratory drive.[25] In fact, both nociception and respiration are moderated by Substance P and NK-1, and in several brainstem sites, nociceptive and chemoreceptive functions converge.[24] Pain is hypothesized to provide tonic increase to the respiratory drive but does not affect chemoreceptor sensitivity. Those with an opioid use disorder and without significant pain are at a greater risk of respiratory depression.

What happens when opioids are used for dyspnea in a controlled medical environment? The use of opioids for symptomatic relief does not significantly change the saturation of oxygen in the blood. In addition, functional studies do not indicate that the use of opioids for dyspnea relief causes high carbon dioxide levels in blood.[26] Opioids, in the doses used for treating dyspnea, do not significantly compromise respiratory function.[27] So far, opioids have the best evidence for providing relief for shortness of breath in advanced disease,[28] but nonpharmacological therapies are also helpful.

One issue to be mindful of is obstructive sleep apnea because opioids relax upper airway muscles and can worsen sleep-disordered breathing, as can other CNS depressants. The STOP-Bang screening questionnaire (http://www.stopbang.ca/osa/screening.php) can be used to identify those at risk so this can be addressed prior to starting opioids.[29]

An office handout that outlines side effects, warns against sharing opioids, and advises using safe and secure storage is an aide memoire and a record of what has been discussed. The National Opioid Use Guideline Group has a reasonable list of issues that patients should know about when taking opioids; office handouts can be made based on the "Are you taking opioids (painkillers) for your pain?" resource available from the Michael G. DeGroote National Pain Centre at McMaster University.[30]

Opioid titration

Opioids should be titrated to the best analgesia with the fewest side effects. In older adults, it is rare that dosages above 90 mg morphine milligram equivalents (MME) per day are used, but in younger patients with faster metabolism, this may be exceeded. The 90 MME per day is not a set limit, but justification is required for exceeding what is considered a threshold of increased risk for adverse events. Continuing improvement in pain and function in the patient, with no evidence of aberrant drug-taking behaviors and with normal urine drug screens, should be documented. If the opioid is being titrated up with increasing intolerable side effects or waning analgesia, clinical judgment should be used to reduce it to a lower dose and be satisfied with that balance, or to rotate to another opioid in search of a better fit for the individual. Switching opioids can be challenging, so a pharmacist or colleague with added training should be asked to assist.

The opioids of first choice in older adults and those with renal failure are fentanyl, methadone, and the buprenorphine patch.

Pain and mental illness

Persistent pain is rarely eliminated, but if quality of life can be improved and the patient feels they are in control of the pain (versus being controlled by it), then there will be a good outcome. Opioids alone may not improve function, especially if other issues such as mental illness, psychological fears, or cognitive impairment are present. Addressing these issues is essential for controlling pain and improving function. Many patients need physical, psychological, and psychiatric assistance; therefore, a team approach to pain management is the best. The patient needs to commit to addressing the interrelated issues. With patients in long-term care, improved function is often not measurable or possible, so improved quality of life, socialization, and cognition should be considered.

Case data

Patient B, living with severe frailty

Patient B, an 89-year-old man living in long-term care, has chronic obstructive pulmonary disease and non-insulin-dependent diabetes, resulting in moderate vascular dementia, renal failure, and peripheral neuropathy. Patient B has family and caregivers who are aware that he used to speak of his painful neuropathy, but now his cognition impairs any reliable information about his pain. Staff have noticed he is agitated with care and resistant to getting dressed and walking. He is not socializing—something he used to enjoy. His care aides have tracked this behavior on the Non-Communicative Patient's Pain Assessment Instrument (NOPPAIN) scale indicated for use in cognitive impairment.[31] The NOPPAIN is a care aide–administered tool for assessing pain behaviors in patients with dementia. The tool focuses on observation of specific pain behaviors while doing common care tasks (https://bcpsqc.ca/wp-content/uploads/2018/11/NOPPAIN.pdf). Over the weekend, an on-call physician ordered loxapine 2.5 to 5.0 mg twice daily to manage his agitation. This is in addition to his metformin, ipratropium, tiotropium, budesonide, nortriptyline, acetaminophen, rabeprazole, and hydromorphone 0.5 mg orally as needed. Recent bloodwork shows his estimated glomerular filtration rate is 32, and his A1c is stable at 7. His family reports that he is not his usual self and is talking about dying.

Trial of opioids for neuropsychiatric symptoms

As cognition declines, so does verbalization of pain, which results in undertreatment of pain in patients with dementia.[32] Observation and attention to behavior helps in recognizing unmet needs and addressing them. Following the behaviors of the patient that are believed to be a sign of pain through a trial of analgesics helps in systematically identifying whether the trial is working.

A trial of opioids is warranted if pain is suspected and there is no improvement with acetaminophen. Why not use nonsteroidal anti-inflammatory drugs (NSAIDs) next? The American Geriatrics Society recommends that the chronic use of all NSAIDs, including high-dose aspirin, should be avoided because of the risk of gastrointestinal bleeding, renal failure, and cardiovascular events.[33] NSAIDs are not safe for persistent pain, and their associated morbidity and mortality in older adults has been extensively reviewed.[34] A study of patients with moderate agitation who were randomly assigned to a stepwise protocol that included strong opioids versus regular care showed that agitation was significantly reduced ($P < 0.001$) in the intervention group compared to the control group.[35] There was no effect on cognition or activities of daily living in the study, meaning that opioids did not control the agitation through sedation.

A trial of opioids includes choosing an opioid that is best suited to older adults, starting at low doses and titrating up while observing behavior. It is challenging for nurses in long-term care to administer short-acting opioids every 4 hours due to high patient-to-nurse ratios. Starting with a low-dose, long-acting opioid can result in better compliance and fewer side effects. There are fewer serum fluctuations with long-acting opioids, which results in less sedation. Low-dose, long-acting oxycodone 5 mg every 12 hours and fentanyl 6 mcg patch (half a 12 mcg patch) are low starting doses that a patient who has significant pain and is receiving several as-needed hydromorphone doses (or Tylenol #3) may be able to transition to. A buprenorphine patch can be started on an opioid-naive patient. If other CNS depressants have been started for pain or agitation (neuroleptics, gabapentinoids, nabilone), the dose should be reduced or they should be discontinued when starting the opioid. A detailed article on pain management in long-term care is available.[36]

A frail patient on opioids who has an infection or is dehydrated may appear opioid toxic because the opioid is not being excreted quickly enough. The patient, who was doing well on low-dose oxycodone for dyspnea from chronic obstructive pulmonary disease and heart failure, may now appear opioid toxic. It is a reflex to stop the opioid, but the patient will have withdrawal in addition to all their other symptoms, which will add to their suffering. The dose should be reduced to half, the patient should be rehydrated until they recover, and then the dose should be adjusted back again if appropriate.

Opioids, in the doses used for treating dyspnea, do not significantly compromise respiratory function.

Reducing polypharmacy

One medication should be trialed at a time. If a drug is not effective, it should be stopped. The "kill two birds with one stone" approach should always be used. If the patient has anxiety/depression and neuropathic pain "birds," an antidepressant could be used as the treatment "stone" for pain and depression. Serotonin-noradrenaline reuptake inhibitors, as well as mirtazapine, are effective adjuvants in neuropathic pain and are better tolerated than tricyclics.[37]

Patients A and B

Patient A trialed oxycodone up to a dose of 20 mg every 12 hours, which worked for the pain but caused severe constipation, even with multiple laxatives. She did much better on the oxycodone/naloxone combination product, but over time her pain grew worse. The 30 mg of oxycodone/naloxone did not improve her pain, likely because the naloxone dose was high enough to interfere with the oxycodone. She was switched to methadone and titrated to a dose of 7 mg every 12 hours with good pain control and manageable side effects. Patient B was started on a buprenorphine patch and was titrated to a 20 mgm/h patch with some reduction in agitation. A higher dose was not recommended, so he was switched to a fentanyl patch at 12 mcg and was titrated up to 18 mcg/h with less agitation and a greater willingness to socialize and exercise.

Summary

Early intervention in older adults with persistent disabling pain may prevent increasing frailty and loss of independence. Opioids are a reasonable choice in older adults with moderate to severe disabling pain that does not respond to acetaminophen or other interventions. When cognition declines, so does the ability to report pain. Titrating analgesics—including opioids—while observing needs-driven distress behavior is the best approach to achieving symptom control and better quality of life.

Refer to the pharmacy detailing booklet (https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/provincial-academic-detailing-service/opioids-drug-booklet.pdf) for a complete list of opioids that are available in BC. ■

Competing interests

None declared.

References

1. Reuben DB, Herr KA, Pacala JT, et al. Geriatrics at your fingertips. 23rd ed. New York: American Geriatrics Society; 2021.
2. Nakai Y, Makizako H, Kiyama R, et al. Association between chronic pain and physical frailty in community-dwelling older adults. Int J Environ Res Public Health 2019;16:1330.
3. Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. Br J Clin Pharmacol 2013;75:60-78.
4. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician 2008;11(suppl 2):S133-S153.
5. Barnett M. Alternative opioids to morphine in palliative care: A review of current practice and evidence. Postgrad Med J 2001;77:371-378.
6. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613-624.
7. Bowie MW, Slattum PW. Pharmacodynamics in older adults: A review. Am J Geriatr Pharmacother 2007;5:263-303.
8. Niscola P, Scaramucci L, Vischini G, et al. The use of major analgesics in patients with renal dysfunction. Curr Drug Targets 2010;11:752-758.
9. Coluzzi F, Caputi FF, Billeci D, et al. Safe use of opioids in chronic kidney disease and hemodialysis patients: Tips and tricks for non-pain specialists. Ther Clin Risk Manag 2020;16:821-837.
10. Patel JN, Hamadeh IS. Pharmacogenomics-guided opioid management. BMJ Support Palliat Care 2020;10:374-378.
11. Gaedigk, A, Sangkuhl, K, Whirl-Carrillo, M, et al. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med 2017;19:69-76.
12. MacDonald N, MacLeod SM. Has the time come to phase out codeine? CMAJ 2010;182:1825.

13. Fulton C, Zang Y, Desta Z, et al. Drug-gene and drug-drug interactions associated with tramadol and codeine therapy in the INGENIOUS trial. Pharmacogenomics 2019;20:397-408.
14. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 1: Clinical considerations. J Pain Symptom Manage 2001;21:144-150.
15. Dhingra L, Ahmed E, Shin J, et al. Cognitive effects and sedation. Pain Med 2015;16(Suppl 1):S37-43.
16. Lim K-H, Nguyen N-N, Qian Y, et al. Frequency, outcomes, and associated factors for opioid-induced neurotoxicity in patients with advanced cancer receiving opioids in inpatient palliative care. J Palliat Med 2018;21:1698-1704.
17. Corli O, Floriani I, Roberto A, et al. Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV 'real life' trial on the variability of response to opioids. Ann Oncol 2016;27:1107-1115.
18. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.
19. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: Consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008;8:287-313.
20. Lalovic B, Kharasch E, Hoffer C, et al. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. Clin Pharmacol Ther 2006;79:461-479.
21. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
22. Musich S, Wang SS, Schaeffer JA, et al. Safety events associated with tramadol use among older adults with osteoarthritis. Popul Health Manag 2021;24:122-132.
23. Markota M., Rummans TA, Bostwick JM, Lapid MI. Benzodiazepine use in older adults: Dangers, management, and alternative therapies. Mayo Clin Proc 2016;91:1632-1639.

When cognition declines, so does the ability to report pain.

24. Pattinson KTS. Opioids and the control of respiration. Br J Anaesth 2008;100:747-758.
25. Borgbjerg MF, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: A controlled study in human volunteers. Pain 1996;64:123-128.
26. Varkey B. Opioids for palliation of refractory dyspnea in chronic obstructive pulmonary disease patients. Curr Opin Pulm Med 2010;16:150-154.
27. López-Saca JM, Centeno C. Opioids prescription for symptoms relief and the impact on respiratory function: Updated evidence. Curr Opin Support Palliat Care 2014;8:383-390.
28. Maddocks M, Lovell N, Booth S, et al. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. Lancet 2017;390(10098):988-1002.
29. Tan A, Yin JDC, Tan LWL, et al. Predicting obstructive sleep apnea using the STOP-Bang questionnaire in the general population. Sleep Med 2016;27-28:66-71.
30. Michael G. DeGroote National Pain Centre. Are you taking opioids (painkillers) for your pain? Accessed 20 September 2021. https://healthsci.mcmaster.ca/docs/librariesprovider82/2017-opioid-guidelines/are-you-taking-opioids-(painkillers)-for-your-pain-(english)-nov-2017.pdf?sfvrsn=3d18c54d_6.
31. Snow AL, Weber JB, O'Malley KJ, et al. NOPPAIN: A nursing assistant-administered pain assessment instrument for use in dementia. Dement Geriatr Cogn Disord 2004;17:240-246.
32. Guerriero F, Sgarlata C, Maurizi N, et al. Pain management in dementia: So far, not so good. J Gerontol Geriatr 2016;64:31-39.
33. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227-2246.
34. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging Dis 2018;9:143-150.
35. Husebo B, Ballard C, Sandvik R, et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: Cluster randomised clinical trial. BMJ 2011;343:d4065.
36. Gallagher R. Practical and strategic pain management in residential care. BCMJ 2013;55;85-89.
37. Fennema J, Petrykiv S, de Jonge L, Arts M. Efficacy and safety of antidepressants as analgesics in chronic pain: A review. Eur Psychiatry 2017;41:S234.