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TOLERABILITY OF OPIOIDS IN OLDER ADULTS: FOCUS ON NEUROTOXICITY

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Abstract

Opioid medications are commonly prescribed for older adults for treatment of chronic pain. Opioids are associated with various side effects including constipation, nausea, and dizziness, as well as delirium, falls, fractures, and motor vehicle crashes. This article will provide a hypothetical but plausible case presentation involving opioid-induced neurotoxicity, a less common but clinically significant adverse drug reaction (ADR). Chronic pain is multifaceted and requires a multimodal and multidisciplinary approach incorporating both non-pharmacologic and pharmacologic therapies. As older adults are at higher risk for opioid-associated adverse effects, close monitoring of side effects is critical.

This article has been peer reviewed.

Conflict of Interest: None

This article was published in December 2021.

Key words:
opioids, pain, older adults, neurotoxicity, delirium

Key Points

- Chronic pain and opioid use in the elderly is common and increasing. Monitoring efficacy and early recognition and management of ADRs through regular evaluation is important for patients on chronic opioid therapy. Particular attention should be focused on mobility and functional changes, weight loss, and falls.
- Older adults are at greater risk for ADRs including toxicity due to drug-drug interactions, multimorbidity, and age-related physiologic changes. The most common opioid associated ADRs include constipation, nausea, and dizziness; serious ADRs include falls, delirium, respiratory depression and sedation.
- Opioid rotation is indicated for opioid-induced neurotoxicity (OIN).
- OIN is managed with hydration, correcting underlying precipitants, and reducing the calculated equianalgesic dose of the new opioid by 25–50%.

Introduction

Chronic pain is a costly disorder affecting 45–85% of older adults and is associated with considerable morbidity including reduced quality of life, social withdrawal, depression, sleep disturbance, cognitive impairment, disability and malnutrition.[1, 2] Opioids have been used for analgesia for moderate to severe cancer and non-cancer pain for many years. Opioids provide analgesia by acting as agonists at opioid receptors (mu-, delta-, and kappa-opioid receptors), which are present throughout the central and peripheral nervous system.[3]

Canada is the second-largest per capita consumer of opioids in the world.[4] In Canada, compared with all other age groups, people over the age of 65 have consistently received more new opioid prescriptions and have a higher proportion (24.8%) that go on to long-term opioid therapy, which is defined as someone prescribed opioids for 90 days out of a 100-day period.[5] In response to the opioid epidemic, an updated Canadian guideline for opioids for chronic non-cancer pain (CNCP) was published in 2017.[6] Unfortunately, there were no specific recommendations for older adults. As older people are excluded from many medication trials, guidelines developed for adults cannot necessarily be applied to older populations.[7]

Several adverse drug reactions (ADRs) are associated with opioid prescription. Older adults are at increased risk for these adverse effects due to a combination of drug-drug interactions, multimorbidity, and age-related physiologic changes. These ADRs will be discussed further below.

Indications for opioid prescription

Opioids are frequently prescribed for different etiologies of pain. There is strong evidence for their use in chronic cancer pain; however, their use in CNCP is less well established.[8] They are frequently prescribed in the palliative care setting to treat both pain and breathlessness. A conditional recommendation has also been made for opioids in patients with chronic obstructive pulmonary disease (COPD) who experience advanced refractory dyspnea despite optimal therapy.[9]

Evidence from high-quality studies in a recent meta-analysis of patients with CNCP demonstrated that opioid use was associated with statistically significant but small improvements in pain and physical functioning.[10] However, low- to moderate-quality evidence suggests similar associations of opioids with improvements in pain and functioning compared with non-opioid alternatives. As a result, the Canadian guideline for opioid therapy in CNCP recommend a trial of opioids for patients with persistent problematic pain after optimization of non-opioid pharmacotherapy (see **Table 2** below).[6] Additionally, opioids are considered second-line analgesia for neuropathic pain; opioids were found in a meta-analysis to be more effective for pain compared to placebo, in addition to a small effect size in favor of opioids for improved function.[11, 12]

The short-term efficacy of opioids for CNCP in the elderly is established.[2] The evidence for long-term opioid use for managing chronic pain at any age is limited.[10] A systematic review found limited evidence supporting long-term opioid use for CNCP in community-dwelling older adults.[13] It is also important to note that few studies on opioid efficacy are conducted in older adults with severe cognitive impairment, who are more likely to experience untreated pain.[13] Many older adults have comorbidities (heart failure, kidney disease, liver cirrhosis) that preclude the use of many other forms of non-opioid analgesia. Therefore, opioid use for CNCP in older adults may be justifiable when less potent medications have been tried or are contraindicated. Long-term opioid use may be reasonable if it improves quality of life and functional status and is used as part of a comprehensive management plan.[14]

Clinical Case - Part 1

Ms. X. is a 75-year-old female who was referred to Geriatric Medicine regarding cognition and recurrent falls, which included several in-hospital falls. She lives with her family in a bungalow and is functionally independent without any gait aids. She recently stopped driving as she no longer felt safe to drive. Her past medical history is significant for COPD, valvular heart disease, pulmonary hypertension, and chronic pain. She was admitted with decompensated congestive heart failure. She complained of involuntary muscle movements in all her extremities, which caused spontaneous falls without warning. She was irritable and tearful throughout her admission and refused to use any gait aids. On physical examination, she was irritable with mood lability and marked inattention, euvolemic, and had resting positive and postural negative myoclonus in all extremities without any focal neurologic deficits. Myoclonus is a sequence of repeated, often non-rhythmic, brief shock-like jerks due to sudden involuntary contraction (positive myoclonus) or relaxation (negative myoclonus; i.e. asterixis) of one or more muscle.[44] You review her medications and note she has taken MS Contin® (extended-release morphine) 30 mg BID for many years. Laboratory investigations were pertinent for serum creatinine 173 umol/L (baseline 100 umol/L) and urea 16.2 mmol/L, with a normal complete blood count, electrolytes, thyroid-stimulating hormone, liver enzymes and synthetic function. Non-contrast CT head was non-contributory.

Pharmacokinetics and pharmacodynamics of opioids

Opioid medications vary in their pharmacokinetic and pharmacodynamic properties, which in turn affect the tolerability and efficacy of each agent. As one ages, the pharmacokinetic and pharmacodynamic parameters can be significantly impacted to varying degrees, which results in an increased sensitivity to medications in older adults.[15] While oral absorption and distribution are similar between younger and older adults, metabolism and excretion can be greatly altered with age due to decline in organ function, particularly hepatic and renal function.[16] First pass metabolism can be significantly decreased in older adults. As a result, medications that undergo substantial first pass metabolism (i.e. morphine) will have higher bioavailability due to reduced metabolism in the elderly when compared with younger counterparts; this can affect tolerability by increasing risk of ADRs.

Cytochromes P450 (CYPs) are among the principal pathways of drug metabolism for several drugs including opioids, which represents a clinically relevant problem for older adults who take multiple medications.[17] Significant metabolism via CYP pathways will predispose older adults to drug interactions and therefore potential toxicity or decreased efficacy depending on the interacting drugs and the nature of the interaction. Therefore, patients taking CYP inducers and inhibitors should be identified when initiating opioid therapy and monitored closely, especially upon initiation of therapy and dose adjustments of opioids and these medications. Several opioids and their pharmacokinetic properties are listed in **Table 1.**[16, 18, 52] In general, hydromorphone has minimal drug-drug interactions. Morphine primarily undergoes phase II metabolism via UGT2B7; however theoretically 3A4 inhibitors (amiodarone, diltiazem, verapamil, grapefruit juice, antifungals) can increase the morphine bioavailability leading to increased opioid effects. Alternatively, 3A4 inducers (anticonvulsants such as phenytoin) may reduce morphine bioavailability. Codeine has a high potential for drug interactions due to metabolism by both 2D6 and 3A4 isoenzymes. Codeine is converted to morphine via

O-demethylation, which is catalyzed by 2D6. There is strong evidence that 2D6 inhibitors (quinidine, bupropion, fluoxetine, paroxetine) will inhibit morphine production and its opioid effects. Codeine is also metabolized to inactive norcodeine via CYP3A; there is some evidence that 3A4 inhibitors increase codeine and subsequent morphine bioavailability.[50]

Table 1. Pharmacokinetics of selected opioids.

Opioid	Plasma protein binding (%)	Volume of distribution (L/kg)	Half-life (t1/2) (h)	Bioavailability (%)	Phase I metabolism	Phase II metabolism	Major metabolites
Tramadol *(prodrug)*	20	2.6-2.9	6.3-7.7	75 (IR) 85-95 (ER)	**CYP3A4**, **CYP2D6**, CYP2B6		Nortramadol (inactive), *O*-desmethyltramadol (active)
Tapentadol	20	540	4	32	CYP2D6, CYP2C9, CYP2C19	UGT1A9, UGT2B7	Tapentadol O-glucuronide
Codeine *(prodrug)*	7-25	3-6	3-4	53	**CYP3A4**, **CYP2D6**	UGT2B7, UGT2B4	Codeine-6-glucuronide (C6G), morphine, norcodeine (inactive)
Morphine	20-35	1-6	2-4	17-33	CYP3A	UGT1A1	Morphine-3-glucuronide (M3G, neuroexcitatory effects), Morphine-6-glucuronide (M6G, analgesic effects)
Hydromorphone	8-19	4	2-3	24 (IR)	-	UGT2B7, UGT1A3	Hydromorphone-3-glucuronide
Oxycodone	38-45	2.6	3.2-4	60-87	**CYP3A4**, CYP2D6	UGT2B7	Noroxycodone (low analgesic), Oxymorphone (analgesic)
Fentanyl *(TD patch)*	79-87	4-6	20-27	-	**CYP3A4**	-	Norfentanyl (inactive)
Methadone	85-90	1-8	8-59	36-100	**CYP3A4**, **CYP2B6**, CYP2C19, CYP2C9, CYP2D6	-	Inactive metabolites
Buprenorphine *(TD patch)*	96	97-187	26	15	**CYP3A4**, CYP2C8	UGT1A1, UGT1A3, UGT2B7	Norbuprenorphine, Buprenorphine-3-glucuronide, Norbuprenorphine-3-glucuronide

NOTES:

1) **Bolded** = major substrate status for metabolism based on clinically relevant drug interaction potential

2) TD = transdermal

3) UGT = uridine diphosphate glucuronosyltransferase

4) CYP = cytochrome P450

Note: Table 1 created by authors using references 16, 18, 52

Renal function generally decreases with age to varying extents. Clearance of opioids and their active metabolites are impaired as renal function decreases, which increases the risk of toxicity with doses that

would usually be well tolerated in younger adults.[16] The greater the extent of dependence on renal clearance of the opioid or its active metabolites, the greater the impact that decreased renal function will have on the tolerability of the specific opioid. Chronic kidney disease (CKD) is highly prevalent among older adults with approximately 72% of patients with CKD being over the age of 60 years.[19] Despite the high incidence of CKD in older adults, there is limited existing evidence for the safety and efficacy of opioids in this population.[20]

Pharmacodynamic changes that affect drug action also occur with aging. Pharmacodynamic changes are less predictable and there are often altered drug response at usual or lower concentrations.[15] Drug-drug and drug-disease interactions may also alter responses to medications. These changes are complex and depend on variables that are difficult to measure such as receptor function and intracellular response.[16] Among older adults, enhanced pharmacodynamic sensitivity (i.e. more pronounced effects at equivalent doses used in younger adults) is seen with all opioids, which results in prolonged pain relief with lower dosages.[15,16]

Opioid-related adverse drug reactions

As previously mentioned, older adults are at greater risk for opioid-associated ADRs including toxicity due to drug-drug interactions, multimorbidity, and age-related physiologic changes. The most common opioid-associated adverse effects include constipation, nausea, and dizziness.[14] Other ADRs include pruritus, dry mouth, sedation, fatigue, hot flushes, increased sweating, delirium, respiratory depression, urinary retention, hyperalgesia, and opioid endocrinopathy (hypogonadism with sexual dysfunction, dysmenorrhea, reduced bone mineral density, depression, and adrenal insufficiency).[10, 14, 21-23, 45] Opioids alter sleep regulation and can cause sleep disordered breathing, management of which is discussed elsewhere.[6, 24] Opioids are also associated with falls and fractures, especially when combined with other CNS agents such as benzodiazepines (clonazepam), tricyclic antidepressants (amitriptyline) and nonbenzodiazepine receptor agonist hypnotics (zopiclone, zolpidem).[25, 26] The 2019 Beers Criteria® provided new strong recommendations to avoid use of opioids concurrently with benzodiazepines or gabapentinoids due to the increased risk of overdose. Exceptions include when transitioning from the former to the latter or when using gabapentinoids to reduce opioid dose.[27] These concerns need to be balanced with the need to treat chronic pain.

A recent Cochrane review reported on adverse events associated with medium- and long-term use of opioids for CNCP. It demonstrated a 42% higher risk of any adverse event and a 175% increased risk of serious adverse events associated with opioid use when compared to placebo, which corresponded to number needed to harm of 4.20 and 28.71, respectively.[23] There are no evidence-based guidelines for prescribing opioids to manage CNCP in older adults with non-dialysis CKD. However, a recent review on opioid management in older adults with CKD recommended buprenorphine, fentanyl and hydromorphone as the safest opioids in terms of ADRs.[20]

While opioids may be part of an appropriate pain management approach for some people, they come with an increased risk of harms including addiction, dependence and death, especially at high doses.[5] Hospitalizations for opioid poisoning increased by 27% between 2013 and 2017 in Canada.[28] Older adults in Canada represent 30% of all admissions to hospital for opioid poisoning.[46] Additionally, opioid use disorder (OUD) is a growing concern among older adults. As a result, Canadian guidelines on OUD in older adults have been recently published, which is beyond the scope of this paper.[29] A recently published Delph Study developed 130 expert consensus recommendations to promote opioid safety in adults receiving palliative care; many of these suggestions can be applied to older adults receiving chronic opioids in the non-palliative setting.[49]

Non-opioid management for chronic pain

A multimodal and multidisciplinary approach is essential for addressing the multifaceted nature of chronic pain, which includes the biopsychosocial effects of the medical condition on the patient.[30, 31] The American Geriatrics Society updated its guidance on the management of persistent pain in older adults with a specific focus on non-opioid and opioid pharmacotherapy in 2009.[32] Non-opioid pharmacotherapy includes acetaminophen, non-steroidal anti-inflammatories (NSAIDs), antidepressants (serotonergic norepinephrine

reuptake inhibitors [SNRI] and tricyclic antidepressants [TCA]), antiepileptic medications, topical medications (e.g. NSAIDs, lidocaine, and capsaicin).[14, 32]

Non-pharmacologic interventions include (1) physical modalities (i.e. cryotherapy, heat therapy, physical exercise, transcutaneous electrical nerve stimulation (TENS), acupuncture, massage), (2) psychological therapy (i.e. cognitive behavioural therapy (CBT), mindfulness-based stress reduction, reassurance, counseling), and (3) invasive interventional procedures (i.e. intravenous infusions, epidural injections, nerve blocks, spinal cord stimulation).[14, 30, 33] There is evidence supporting biofeedback training in relaxation as well as CBT among nursing home patients.[33, 34] For general pain management strategies to optimize prior to initiating opioid therapy, see **Table 2.**[14, 30-33] Helpful guidance including the evidence, recommended starting doses, and side effects for non-opioid pharmacotherapy have been provided in several reviews.[30,31]

Table 2. Brief summary of non-opioid management for chronic pain

Non-pharmacologic interventions	Non-opioid pharmacotherapy
(1) Physical modalities	**Topical**
Heat therapy	Non-steroidal anti-inflammatory drugs (NSAIDs)
Cryotherapy	Lidocaine
Physical exercise – including Tai Chi, Yoga	Capsaicin
Transcutaneous electrical nerve stimulation (TENS)	
Acupuncture	
Massage therapy	
(2) Psychological therapy	**Oral**
Mindfulness-based stress reduction	Acetaminophen
Relaxation therapies including meditation	NSAIDs including COX-2 inhibitors*
Reassurance	Antidepressants (TCA, SNRI)
Counselling	Antiepileptics (gabapentinoids, carbamazepine)
Biofeedback	Cannabinoids*
Cognitive-behavioural therapy (CBT)	Muscle relaxants*
(3) Invasive interventional procedures	
Intravenous infusions	
Epidural injections	
Nerve blocks	
Spinal cord stimulation	

NOTES:

*Caution with use – special attention to underlying comorbidities, medications, and cognitive impairment

Older adults with functional impairment and/or reduced quality of life due to chronic pain may benefit from a multidisciplinary pain rehabilitation program. These programs provide an integrated, multimodal approach to chronic pain management through education, personal and group therapy, psychology, physical and occupational therapy.[14, 35] Such programs address the various dimensions of pain and often require a physician referral; a list of updated Canadian pain clinics is maintained by the Michael G. DeGroote Institute for Pain Research and Care at McMaster University.[47] Due to the long wait times associated with these programs, primary care physicians can consider referring patients to individual healthcare professionals who have an interest in pain (psychology, occupational and physical therapist).

There remains a significant role for interventional therapies for managing CNCP in older adults, who often suffer from degenerative disorders that may not amenable to surgical repair. Relatively low-risk injections and minimally invasive surgical implants can significantly reduce the need for pharmacotherapy, including opioids.[14] Interventional pain management is beyond the scope of this paper, but the Canadian Pain Society Special Interest Group on Neuropathic Pain (NePSIG) has previously reported evidence-based guidelines on interventional neuropathic pain treatments.[36] These therapies are usually considered when standard pharmacologic treatment fails and are typically ordered and frequently performed by pain specialists.

Return to Clinical Case - Part 2

Collateral history from family revealed similar sporadic episodes of involuntary muscle movements in the preceding year causing falls-related admissions. A diagnosis of hypoactive delirium secondary to opioid-induced neurotoxicity in the context of acute kidney injury was made based on myoclonus and delirium in the context of chronic opioid use after other causes, including primary neurological conditions were excluded. Neurology was consulted for a second opinion and did not feel additional investigations were warranted due to metabolic and toxic etiologies and the absence of any focal neurologic deficit.

Opioid-induced neurotoxicity (OIN)

OIN is a clinical syndrome presenting with a range of cognitive, motor and sensory symptoms including hypersomnolence, delirium, hallucinations, allodynia, hyperalgesia, myoclonus, tremor, and seizures.[37, 38] There is some overlap between OIN and serotonin syndrome, however most cases of the latter begin within 24 hours of increasing a serotonergic agent, overdose, or addition of another serotonergic agent; additional features include autonomic hyperactivity (hyperthermia, tachycardia, mydriasis, diaphoresis, diarrhea) and neuromuscular abnormalities (tremor, myoclonus, hyperreflexia, muscle rigidity).[51] OIN can be challenging to diagnose as it can be misinterpreted as disease progression in cancer and palliative patients.[38] Neurotoxicity can occur with any opioid, but it is most commonly associated with those that form active metabolites such as meperidine, morphine, oxycodone, and hydromorphone.[38, 39] Risk factors for OIN include high dosage of opioids, dehydration, renal failure, infection, end-stage disease and advanced age due to increased risk of metabolite accumulation.[38, 40]

The pathophysiology of OIN is poorly understood. It is largely accepted that the accumulation of active glucuronidated morphine and hydromorphone metabolites is responsible for many cases of OIN.[41] Additional etiologies are suspected as neurotoxicity can occur with opioids lacking active metabolites. Hypothesized alternative mechanisms include endocytosis of opioid receptors, activation of N-methyl-D-aspartate (NMDA) receptors, and opioid-induced effects on inhibitory and excitatory neurotransmitters including acetylcholine and dopamine.[40]

There are a limited number of studies on OIN; therefore, data are lacking on the incidence of OIN, especially in the non-palliative setting.[3] OIN was observed in 15% of cancer patients receiving opioids as part of inpatient palliative care. Delirium was the most common symptom, whereas myoclonus occurred in 47% of patients.[38] Current evidence for OIN in patients with renal impairment consists of very low-quality studies with hospice or palliative care patient populations[42]. One prospective study found that 26% of 109 patients receiving morphine for chronic-malignancy related pain developed myoclonus.[43]

OIN is managed with dose reduction or discontinuation of opioids, opioid rotation (changing one opioid to another in order to improve pain control or reduce unwanted side effects), hydration and correction of underlying precipitants such as renal impairment.[3] If performing an opioid rotation due to intolerable side effects, it is recommended to reduce the calculated equianalgesic dose of the new opioid by 25–50% to minimize the risk of inadvertent overdose.[6] For equianalgesic dosing of different opioids, see **Table 3**.

Table 3. Opioids and approximate equianalgesic doses (mg).

Generic Name	IM/SC	PO
Tramadol		175-300
Tapentadol		150
Codeine	120	200
Morphine	10	20-30
Hydromorphone	2	4-6
Oxycodone		10-15
Fentanyl	0.1	
Methadone		3
Buprenorphine sublingual		0.375
Adapted from The Ottawa Hospital. The Ottawa Hospital Formulary; Ottawa, Ontario; 2016.		

Case - Part 3

The patient was managed with opioid rotation to hydromorphone with 25% dose reduction (morphine 30 mg BID was stopped and hydromorphone 2 mg q6h was started simultaneously), reduced diuresis, and subsequent transfer to the Geriatric Medicine Unit. Over the course of 1 week, her myoclonic jerks completely stopped with rotation, and with resolution of her acute kidney injury and delirium. She was discharged on oral hydromorphone with Cardiology follow-up.

Initiating, monitoring, and deprescribing opioids

It is important to not initiate opioid therapy for CNCP unless non-opioid pharmacologic and non-pharmacologic options have been optimized as these modalities may achieve a similar magnitude of improvement in pain and function more safely without the risk of opioid-related ADRs.[6] When initiating opioids for CNCP, it is recommended to use the lowest possible dose and titrate up based on tolerability and efficacy with close follow-up.[16]

As with all medication, long-term opioid use should be regularly evaluated to determine efficacy, tolerability, indication, as well as counselling on the benefits and harms of ongoing treatment. No specific monitoring intervals were recommended in the Canadian guideline for opioid therapy and CNCP, however the CDC recommends clinicians consider follow-up within 1–4 weeks of dose escalation or when total daily opioid dosage is >50 morphine milligram equivalents (MME)/day.[6,48] Do the ADRs outweigh the benefits of treatment? Once determined that deprescribing is appropriate, initiation of tapering depends on the dose and the duration of opioid use. Currently, there are no Canadian validated opioid tapering protocols or algorithms. For general strategies to consider when initiating opioid tapering, see **Table 4**.

Table 4. General strategies of opioid tapering.

Establish a supportive and trusting relationship with the patient and/or substitute decision maker. Obtain buy-in in order to maximize chances of successful opioid reduction.
Ensure a multimodal pain management approach exists with optimization of non-pharmacologic and non-opioid pharmacologic therapy.
Continue with the same opioid when possible. This facilitates accurate calculation of opioid use and appropriate titrations. Opioid rotation is sometimes necessary, especially when experiencing ADRs. Opioids and their equianalgesic doses are listed in **Table 3.**
A gradual dose reduction of 5–10% of the morphine equivalent dose every 2–4 weeks with frequent follow up is a reasonable rate of opioid tapering.[6]
If withdrawal symptoms develop, return to the previous tolerated dose and extend the tapering interval.
In a tapering regimen, prescribing as needed (PRN) doses is discouraged to promote adherence.
If the patient is taking a sustained release product, it will eventually be necessary to switch to an immediate acting product to facilitate further decreases.

Monitoring is a key aspect of the deprescribing process. Depending on the individual situation, withdrawal symptoms can develop within 1 to 3 days of dose reductions, whereas recurrent pain may occur within 1 to 2 weeks of dose reductions. If pain or withdrawal symptoms develop, extend tapering intervals and consider pausing until pain stabilizes and PRN use decreases. If patients are experiencing serious challenges with tapering, a referral should be made to a formal multidisciplinary program.[6]

Rotation to or from transdermal fentanyl requires carefully monitoring as wide variations on dosing equivalencies have been reported. There is more guidance with respect to conversion from oral opioids to transdermal fentanyl (as opposed to rotating from transdermal fentanyl to oral opioids), which is listed in **Table 5**. It should be noted that recommendations are not reciprocal (i.e. recommendations for converting oral opioids to transdermal fentanyl should not be used to convert transdermal fentanyl to oral opioids as the conversion to fentanyl is conservative and could overestimate the dose of the new agent).

Table 5. Converting from current opioid to transdermal fentanyl.

Current Analgesic	Daily Dosage (mg/day)						
Oral Morphine	60-134	135-179	180-224	225-269	270-314	315-359	360-404
IM/IV Morphine[1]	20-44	45-60	61-75	76-90	NA[2]	NA[2]	NA[2]
Oral Oxycodone	30-66	67-90	91-112	113-134	135-157	158-179	180-202
Oral Codeine	150-447	448-597	598-747	748-897	898-1047	1048-1197	1198-1347
Oral Hydromorphone	8-16	17-22	23-28	29-33	34-39	40-45	46-51
IV Hydromorphone	4-8.4	8.5-11.4	11.5-	14.5-	16.6-	19.6-22.5	22.6-25.5
	↓	↓	↓	↓	↓	↓	↓
Recommended Fentanyl Transdermal[3,4,5]	25 mcg/hr	37 mcg/hr	50 mcg/hr	62 mcg/hr	75 mcg/hr	87 mcg/hr	100 mcg/h

NOTES:
1) Using 1:3 parenteral to oral dose ratio.
2) NA: not available, meaning that there is insufficient data available for guidance.
3) This conversion table uses conservative equivalent dosage and therefore the safety factor dose reduction is not necessary.
4) The 12 mcg/hr dose is not included in this table because it generally should not be used as the initiating dose, except in the case of patients for whom clinical judgement deems it appropriate to start at less than 25 mcg/hr.

5) Fentanyl transdermal at any dose is contraindicated in opioid-naïve patients.

Adapted from The Ottawa Hospital. The Ottawa Hospital Formulary; Ottawa, Ontario; 2015.

The 12 µg/hr patch is typically used for titrating doses up or down, but can be considered for the frail older patient, patient with advanced CKD where hydromorphone is poorly tolerated, or in patients taking a 3A4 inhibitor where a lower dose of fentanyl may be warranted.

Conclusion

Older adults have increased susceptibility to opioid-related ADRs, but many substantially benefit from appropriate prescribing. It is important for opioid-prescribing physicians to regularly reassess management and understand how to recognize and manage anticipated ADRs. Additionally, careful monitoring of efficacy and tolerability by the entire medical team (physician, pharmacist, nurse, patient and family) is critical. One must consider opioid reduction and/or rotation in older adults experiencing unexplained symptoms such as delirium, hyperalgesia, and involuntary muscle movements.

To optimize pain, quality of life, and function, a multimodal approach incorporating both non-pharmacologic and pharmacologic treatment is strongly recommended. Certain patients may benefit from referral to a multidisciplinary pain rehabilitation program, which may incorporate minimally invasive interventional procedures.

The potential adverse health consequences combined with the prevalence of opioid use in the elderly suggest the need for more targeted and evidence-based treatment of chronic pain in older adults. Future studies should evaluate both opioid efficacy in terms of pain reduction, physical functioning and psychosocial well-being, as well as the incidence of opioid-related ADRs including OIN.

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