Opioid use for chronic non-cancer pain in the frail elderly

Uso de opióides para o tratamento da dor crónica não oncológica no idoso frágil

Beatriz Braga* and Nuno Almeida

Serviço de Medicina Interna do Hospital do Divino Espírito Santo de Ponta Delgada, E.P.E., Portugal

Abstract

Pain is a prevalent symptom in the elderly, and in this group of patients, about 20% are medicated with analgesics. The frailty syndrome comprises a reduction of lean body mass, sarcopenia, chronic malnutrition, and a reduction in mobility. It is essential to control chronic pain in the elderly to ensure quality of life and an active role in the family and society. With aging, there are multiple physiological changes that occur in the human body, and it is imperative to take these factors into account when prescribing drugs to elderly patients, namely, opioid analgesics. To date, there are few randomized clinical trials to study opioid therapy in elderly population. The authors propose to make a bibliographical review of the available references about this subject, to improve clinical practice.

Key-words: Opioid. Elderly. Frailty.

Resumo

A dor é um sintoma prevalente nos idosos, sendo que neste grupo de doentes cerca de 20% encontra-se medicado com analgésicos. A síndrome de fragilidade pode ser descrita como uma redução da massa magra corporal, sarcopenia, sub-nutrição crónica e uma redução na performance em termos de mobilidade. É essencial controlar a dor crónica nos idosos, de forma a assegurar a qualidade de vida e um papel ativo na família e na sociedade. Com o envelhecimento, são múltiplas as alterações fisiológicas que acontecem no corpo humano, e é imperativo ter estes fatores em conta aquando da prescrição de fármacos a doentes idosos, nomeadamente analgésicos opióides. Até à data, existem poucos estudos clínicos randomizados de forma a estudar a terapêutica opióide na população idosa. Os autores propõem-se a realizar uma revisão bibliográfica às referências disponíveis acerca deste tema, de modo a auxiliar na prática clínica.

Palavras-chave: Opióides. Idoso. Fragilidade.

Introduction

Pain is prevalent in older people and has significant detrimental effects on function and quality of life. Epidemiological studies have estimated that approximately 20% of people in this age group are taking

analgesic medicines and the majority are using these medications for greater than 6 months' duration¹.

Frailty syndrome has been described in terms of an excessive reduction of lean body mass, sarcopenia, chronic undernourishment, a reduction in walking performance and mobility, and poor endurance associated

Correspondence:

Beatriz Braga

E-mail: beatriz.p.braga@azores.go

0872-4814/© 2019 Associação Portuguesa para o Estudo da Dor. Published by Permanyer. This is an open access article under the terms of the CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Date of reception: 04-07-2019

Date of acceptance: 03-12-2019

DOI: 10.24875/DOR.M20000001

Available online: 11-12-2020

DOR. 2020;27(1):9-14

www.dor.pt

Table 1. Physiologic changes with aging and effects (*adapted*^{9,10}).

System	Changes	Effect	Effect on drug use
General	Increased body fat Decreased body water	Increased volume of distribution for lipophilic medication Increased plasma concentration of hydrophilic drugs	Delayed elimination and onset of drug action Higher frequency of side effects
Gastrointestinal	Altered secretions and mobility Altered blood flow and absorptive surface	Altered drug absorption, bioavailability, transit time Enhanced opioid-related bowel dysmotility	Altered oral bioavailability
Hepatic	Reduced hepatic blood flow Decreased hepatic enzymes, protein synthesis, regeneration rate	Decreased serum albumin Decreased drug metabolism by 30-40%	Increased bioavailability Higher toxicity risk
Cardiac	Decreased cardiac index	Rapid and high drug peak	Higher toxicity risk
Renal	Decreased renal blood flow Reduced renal function	Decreased renal elimination	Required dose adjustments
Nervous system	Decreased cerebral blood flow Neuronal loss Decreased synthesis of neurotransmitters Decreased opioid receptor density	Decreased descendent inhibitory pain control Altered pain processing	Increased pain with noxious stimuli Altered response to pain
Muscle	Decreased muscle mass	Decreased functioning	

with a perception of exhaustion and fatigue¹. It can be diagnosed on presence of three out of these five factors: unintentional weight loss, extreme fatigue, weakness in hand grip, slowed walking speed, and low physical activity in older adults². It is a complex, multifactorial, and dynamic state characterized by decreased energetic and homeostatic reserve and an increased vulnerability to stressors. Pain remains the most common complaint in this group. Although frail older people have an increased susceptibility to the adverse effects of analgesics, analgesic medicines can still be used safely and effectively^{1,3}.

The pathophysiologic profile of older adults changes with age (Table 1). Decline in organ function dictates the pharmacokinetic properties of many drugs⁴. Absorption can also be altered, and there are changes in body composition: increase in adipose tissue, decrease in body mass, and decrease in body water, which can influence drug distribution⁵. The first-pass metabolism of opiate metabolism can be reduced in older age as in liver diseases like cirrhosis⁶. Furthermore, decreased glomerular filtration rate can lead to accumulation of opioid metabolites and to more adverse effects. Protein binding could represent an important site of interaction^{7,8}.

Treating and controlling chronic pain is essential in elderly patients to maintain a good quality of life and an active role in both the family and society. To date,

there are only a few randomized clinical trials testing opioid therapy in elderly patients^{3,7,11}.

OPIOID use

The WHO three-step “analgesic ladder” is also recommended for the geriatric population. The selected medication should be started at the lowest effective dose followed by a gradual and slow titration of dosage. There should be adequate intervals between the escalations of medication during titration^{7,9,12}.

Significant pharmacokinetic and pharmacodynamic changes that occur with advancing age increase the risk of adverse effects of opioids. There are also some discrepancies between guidelines, which recommend the use of lower doses of opioids in older patients¹³, and the findings in the literature that suggest that pain is often undertreated in this age group. Morphine, fentanyl, oxycodone, and buprenorphine are still the preferred evidence-based choices for add-on opioid therapy for these patients⁷. Morphine or oxycodone at a dose of 2.5 mg every 6 h with a plan to follow up within 48-72 h to assess for efficacy and adverse effects represents a reasonable starting regimen for patients with moderate to severe pain. Opioids should be started at 25-50% of the recommended dose for adults^{8,13} and the clinician should always balance pain relief with adverse effects.

Table 2. Characteristics of commonly prescribed opioids in older adults (*adapted*^{13,18}).

Opioid	Potency	Metabolism/excretion	Common side effects	Additional considerations	Initial low dose	Maximum dose in elderly patients
Tramadol	Weak	Hepatic/renal	Constipation, nausea, appetite loss, drowsiness, dizziness, sweating	Lowers seizure threshold, may precipitate serotonin syndrome	Tramadol with acetaminophen: 37,5 mg orally every 6h If CR: 100-150 mg/d orally	8 tablets/d 300 mg/d for older than 75 years; 150 mg if Undernourished or cachectic
Codeine with acetaminophen	Weak	Hepatic/renal	Also falls	Variability in response due to variability in metabolism Combination with acetaminophen increases analgesic efficacy	15-30 mg orally every 6-8h	240 mg
Morphine	Strong	Hepatic/renal	Constipation, nausea, vomiting, appetite loss	Metabolites accumulate in renal insufficiency	If IR: 2,5-5 mg orally every 4-8h If CR: 10 mg orally every 12h, 10-20 mg orally every 24h	
Hydromorphone	Strong	Hepatic/renal	Constipation, dizziness, drowsiness, dry mouth	Safer in renal insufficiency	4 mg orally every 24h	
Fentanyl	Strong	Hepatic/renal	Anxiety, confusion, constipation, headache, indigestion, nausea	Prolonged elimination No initiation in an opioid-naïve patient Onset delayed by 12-24h	Fentanyl patch: 12-25 ug/h every 72h Allow 6 or more days before increasing dose	
Buprenorphine	Strong	Hepatic/renal	Less constipation, nausea and respiratory depression	Use safely in renal failure May be initiated in opioid-naïve patients	Buprenorphine patch: 5 ug/h every 7d	20 ug/h

IR: immediate release; CR: controlled release.

After successful initiation of a short-acting opioid, a sustained-release preparation can be considered to decrease medication complexity. Immediate-release medications should be continued to control breakthrough or incident pain at a dose typically 10% of the total 24-h sustained release dosage¹³.

Canadian guidelines for the safe and effective use of opioids for chronic non-cancer pain concluded that opioid therapy for elderly patients can be safe and effective with appropriate precautions, including lower starting doses, slower titration, long dosing intervals, more frequent monitoring, and tapering of benzodiazepines¹⁴.

The time to maximal effect of opioids does not change with aging¹³. The transdermal route is suited for the elderly as it provides ease of use for the patient and the caretaker, provides greater adherence to prescribed regimens, and has less risk of toxicity and dose

dumping. A transdermal delivery system is also useful when elderly patients are unable to tolerate oral medications or are unwilling to swallow oral medications. Transdermal medications also avoid needle punctures associated with subcutaneous or intravenous routes and are less labor intensive than these routes¹⁵. Most opioids can also be given in liquid form or through subcutaneously or inhaled routes¹⁶.

Essentially, all patients with moderate-severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy¹⁷. Some characteristics of commonly prescribed opioids in older adults are described in [table 2](#).

There has to be some particular attention to patients with renal and/or hepatic impairment. [Table 3](#) was based on information gathered in Lexicomp^{®19}, according to the manufacturer's labeling.

Table 3. Dose adjustments in commonly prescribed opioids in older adults (*adapted*¹⁹).

Opioid	Renal impairment	Hepatic impairment
Tramadol	<p>Immediate release formulations - if GFR $\geq$ 30 mL/minute there are no dosage adjustments provided, use with caution; if GFR $<$ 30 mL/minute increase dosing interval to every 12 hours (maximum: 200 mg/day).</p> <p>Extended release formulation - if GFR $\geq$ 30 mL/minute, there are no dosage adjustments provided, use with caution; if GFR $<$ 30 mL/minute, avoid use.</p>	<p>Immediate release: There are no dosage adjustments provided. Cirrhosis: 50 mg every 12 hours.</p> <p>Extended release: Child-Pugh class A and B: There are no dosage adjustments provided, use with caution. Child-Pugh class C: Avoid use.</p> <p>Elderly $>$ 75 years: Immediate release: Maximum: 300 mg/day. Extended release: Use with extreme caution.</p>
Codeine	<p>There are no dosage adjustments provided; however, clearance may be reduced and active metabolites may accumulate in patients with renal failure. Initiate at lower doses or longer dosing intervals followed by careful titration. Alternate recommendations: GFR $>$ 50 mL/minute: No dosage adjustment necessary. GFR 10 - 50 mL/minute: Administer 75% of dose. GFR $<$ 10 mL/minute: Administer 50% of dose. Continuous renal replacement therapy: Administer 75% of dose; titrate.</p>	<p>There are no dosage adjustments provided; however, lower initial doses or longer dosing intervals followed by careful titration are recommended.</p>
Morphine	<p>No specific dosage adjustments are provided. The choice of an alternate opioid may be prudent in patients with baseline renal impairment or rapidly changing renal function especially since other analgesics may be safer and reduced initial morphine dosing may result in suboptimal analgesia. Although clearance of morphine is similar to patients with normal renal function, glucuronide metabolites accumulate in renal impairment resulting in increased sensitivity.</p>	<p>There are no dosage adjustment provided. Pharmacokinetics unchanged in mild liver disease; substantial extrahepatic metabolism may occur. Cirrhosis: dosage adjustment required.</p>
Hydromorphone	<p>Hydromorphone ER: GFR $>$ 60 mL/minute: No dosage adjustments provided. GFR 40 - 60 mL/minute: Initiate with 50% of the usual starting dose for patients with normal renal function. Use with caution and monitor closely. GFR $<$ 30 mL/minute: Initiate with 25% of the usual starting dose for patients with normal renal function. Use with caution and monitor closely.</p>	<p>Hydromorphone ER: Mild impairment: No dosage adjustments provided. Moderate impairment: Initiate with 25% of the usual starting dose for patients with normal hepatic function. Use with caution and monitor closely. Severe impairment: Use alternate analgesic.</p>
Fentanyl	<p>Transdermal (patch): Mild-to-moderate impairment: Reduce dose by 50%. Severe impairment: Use not recommended. Transmucosal and intranasal: There are no dosage adjustments provided, use with caution. Although fentanyl pharmacokinetics may be altered in renal disease, fentanyl can be used successfully in the management of breakthrough pain.</p>	<p>Transdermal (patch): Mild-to-moderate impairment: Reduce dose by 50%. Severe impairment: Use not recommended. Transmucosal: There are no dosage adjustments provided, use with caution. Although fentanyl pharmacokinetics may be altered in hepatic disease, fentanyl can be used successfully in the management of breakthrough pain. Elderly have been found to be twice as sensitive as younger patients to the effects of fentanyl. Transmucosal (eg., Actiq): Patients $>$ 65 years of age were titrated to a mean dose that was 200 mcg less than that of younger patients.</p>
Buprenorphine	<p>No dosage adjustments for renal impairment (has not been adequately studied), use with caution. Note: Buprenorphine cannot be dialyzed.</p>	<p>In mild hepatic impairment, there is no dosage adjustment necessary. In moderate impairment, use with caution during maintenance treatment. In severe hepatic impairment, use is not recommended.</p>
Tapentadol	<p>GFR $\geq$ 30 mL/minute: No dosage adjustment necessary. GFR $<$ 30 mL/minute: Use not recommended.</p>	<p>Child-Pugh class A: No dosage adjustment necessary. Child-Pugh class B: Immediate release form - initial dose 50 mg every 8 hours or longer (maximum: 150 mg/24 hours). - extended release: Initial 50 mg every 24 hours or longer; maximum: 100 mg/day Child-Pugh class C: Use not recommended.</p>

GFR : Glomerular filtration rate.

Proper dosing of opioids can be achieved in older people by starting with a short-acting opioid and rapidly switching to a controlled-release formulation, with emphasis on regular dosing schedule. Solely “prn” dosing should be avoided. Instead, such dosing should be used only for rescue of breakthrough pain. A general rule is to increase regular dosages if “prn” medication is used 3 times over a 24 h period. It is helpful to think of “prn” as standing for “pain relief negligible,” keeping in mind that regular dosing uses less narcotic and provides better pain relief¹⁷.

There can be interaction with benzodiazepines. This is related to the synergistic effect on the CNS causing sedation and respiratory depression¹⁵.

A paper that analyzes the tolerability and analgesic efficacy of tapentadol extended release (ER) compared with oxycodone controlled release (CR) in patients ≥ 75 years of age with moderate to severe, chronic osteoarthritis knee or low back pain, concluded that tapentadol ER (100-250 mg bid) provided significant pain relief compared with placebo and had a better overall gastrointestinal tolerability profile than oxycodone CR²⁰. Tapentadol may prove to be a useful analgesic for the treatment of chronic pain in frail elderly persons because of its possible better gastrointestinal tolerability.

Most of the drugs bind to albumin, but buprenorphine binds to alpha- and beta-globulins. As a result, drug-drug interactions related to protein binding for this drug are small²¹.

The absorption of transdermal buprenorphine among patients varies less than among patients on transdermal fentanyl and buprenorphine is little affected with age so its relative potency will increase in the elderly. It has been suggested that fewer dosage adjustments are needed in patients using transdermal buprenorphine compared with patients using transdermal fentanyl¹⁵.

A literature search was performed for all individual drugs, using a validated and published set of 23 criteria concerning effectiveness, safety, pharmacokinetics and pharmacodynamics, experience, and convenience. Using the set of 23 criteria, no differentiation can be made between the appropriateness of buprenorphine, fentanyl, hydromorphone, morphine, and oxycodone for use in elderly patients²². In the treatment of chronic pain in the frail elderly, the opioids of first choice are buprenorphine, fentanyl, hydromorphone, morphine, and oxycodone²². To improve the convenience for elderly patients, the CR oral dosage forms and transdermal formulations are preferred²².

Due to high fat to protein ratios, opioids in the elderly should be started at doses 25-50% lower than those used in young adults, with rescue doses limited to 5% of the total daily dose available every 4 h^{15,23}.

Conclusion

The use of long-acting opioids may be a relatively safe option in the management of persistent non-malignant pain in the nursing home population, yielding benefits in functional status and social engagement²⁴. According to the available literature, a lower initial dose should be used when prescribing opioids to older patients, in particular in those who are drug naive; longer dosing intervals and slow adjustments of the dosage are also recommended to achieve the optimum therapeutic effect in safety^{24,25}.

Morphine, fentanyl, oxycodone, or buprenorphine are still the preferred evidence-based choices for add-on opioid therapy for older people or frail patients^{13,25}. The metabolism of hydromorphone and oxycodone is directly dependent on liver function, while elimination of morphine depends on renal function. Thus, fentanyl could be a preferential opioid in liver dysfunction, while buprenorphine is the agent of preference for patients with impaired renal function. Morphine and hydromorphone should be used with caution in hepatic and renal impairment²⁶.

References

1. McLachlan AJ, Bath S, Naganathan V, Hilmer SN, Couteur DG, Gibson SJ, et al. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. *Br J Clin Pharmacol*. 2011;71:351-64.
2. Rastogi R, Meek B. Management of chronic pain in elderly, frail patients: finding a suitable, personalized method of control. *Clin Interv Aging*. 2013;8:37-46.
3. Gianni W, Ceci M, Bustacchini S, Corsonello A, Abbatecola AM, Brancati AM, et al. Opioids for the treatment of chronic non-cancer pain in older people. *Drugs Aging*. 2009;26 Suppl 1:63-73.
4. Tumer N, Scarpace PJ, Lowenthal DT. Geriatric pharmacology: basic and clinical considerations. *Annu Rev Pharmacol Toxicol*. 1992;32:271-302.
5. Vaughan C. Development and implementation of a process to ensure safe use of morphine sulfate extended-release liposome injection. *Am J Health Syst Pharm*. 2008;65:458-61.
6. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. *Clin Pharmacokinet*. 1999;37:17-40.
7. Prostran M, Vujovic KS, Vuckovic S, Medic B, Srebro D, Divac N, et al. Pharmacotherapy of pain in the older population: the place of opioids. *Front Aging Neurosci*. 2016;8:144.
8. Tracy B, Morrison RS. Pain management in older adults. *Clin Ther*. 2013;35:11.
9. Rastogi R, Meek BD. Management of chronic pain in elderly, frail patients: finding a suitable, personalized method of control. *Clin Interv Aging*. 2013;8:37-46.
10. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57:1331-46.
11. Paladini A, Fusco M, Coaccioli S, Skaper SD, Varrassi G. Chronic pain in the elderly: the case for new therapeutic strategies. *Pain Physician*. 2015;18:E863-76.
12. Norma da Direção-Geral de Saúde. Orientações Técnicas Sobre o Controlo da Dor Crónica na Pessoa Idosa. Lisboa: Norma da Direção-Geral de Saúde; 2010.

13. Malec M, Shega JW. Pain management in the elderly. *Med Clin N Am*. 2015;99:337-50.
14. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American society of interventional pain physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I-evidence assessment. *Pain Physician*. 2012;15:S1-66.
15. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. *Clin Interv Aging*. 2008;3:421-30.
16. Gloth FM. Pain management in older adults: prevention and treatment. *J Am Geriatr Soc*. 2001;49:188-99.
17. Smith H, Bruckenthal P. Implications of opioid analgesia for medically complicated patients. *Drugs Aging*. 2010;27:417-33.
18. Karras B, McKee N, Regier N, Stone S. Opioids for chronic non-cancer pain in the elderly, an osteoarthritis case. *Can Fam Physician*. 2011;57:907-11.
19. Lexicomp® Database. Available from: <https://www.wolterskluwer CDI.com/lexicomp-online>. [Last accessed on 2019 Jun 02].
20. Biondi DM, Xiang J, Etropolski M, Moskovitz B. Tolerability and efficacy of tapentadol extended release in elderly patients ≥ 75 years of age with chronic osteoarthritis knee or low back pain. *J Opioid Manage*. 2015;11:5.
21. Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, 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.
22. Ojik AL, Jansen PA, Brouwers JR, Roon EN. Treatment of chronic pain in older people evidence-based choice of strong-acting opioids. *Drugs Aging*. 2012;29:615-25.
23. Abraham J. Advances in pain management for older adult patients. *Clin Geriatr Med*. 2000;16:269-311.
24. Bernfort L, Gerdle B, Rahmqvist M, Husberg M, Levin L. Severity of chronic pain in an elderly population in Sweden-impact on costs and quality of life. *Pain*. 2015;156:521-7.
25. Schuler M, Griebinger N. Opioids for non-cancer pain in the elderly. *Schmerz*. 2015;29:380-401.
26. Veal FC, Peterson GM. Pain in the frail or elderly patient: does tapentadol have a role? *Drugs Aging*. 2015;32:419-26.