

Guidance on opioids prescribing for the management of persistent non-cancer pain in older adults

Fabio Guerriero

Fabio Guerriero, Department of Internal Medicine and Therapeutics, Section of Geriatrics, University of Pavia, 27100 Pavia, Italy

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Correspondence to: Fabio Guerriero, MD, PhD, Department of Internal Medicine and Therapeutics, Section of Geriatrics, University of Pavia, via Emilia 12, 27100 Pavia, Italy. fabio.guerriero01@universtidipavia.it
Telephone: +39-0382-381772
Fax: +39-0382-381218

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Abstract

Many older adults suffer from persistent pain but prevalence studies consistently showed high levels of untreated or under-treated pain in old population. Both

persistent pain and pain under-treatment adversely affect independence and quality of life in geriatric patients. Pain management is challenging in this age-group because of the declining organ function, the presence of concurrent diseases and polypharmacy. For all the above reasons, persistent pain in the elderly should be considered a geriatric syndrome per se and effective approaches are warranted. Current guidelines and consensus statements recommend opioid therapy for older adults with moderate-to-severe persistent pain or functional impairment and diminished quality of life due to pain. However clinicians and patients themselves have some concerns about opioids use. Age-related decline in organs functions and warnings about risk of addiction and drug misuse/abuse also in geriatric patients need particular attention for safe prescribing. On the basis of clinical evidence, these practical recommendations will help to improve the competence on opioid role in persistent pain management and the likelihood of a successful analgesic trial in older patients.

Key words: Chronic pain; Opioids; Pain management; Elderly

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Core tip: Persistent pain (pain that lasts more than three months) is a common issue in older adults. Pain management requires a multidisciplinary approach and the knowledge of analgesic drugs is fundamental for effective and safe outcomes. Current guidelines for geriatric patients recommend opioid-use as a first-line agent for moderate-to-severe persistent pain. However some concerns about opioid-use in this age-group are present. Nevertheless opioid epidemic needs attention for safe prescribing. This manuscript addresses to data that will likely help to improve the competence on opioids use and the likelihood of a successful analgesic trial in older adults.

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INTRODUCTION

Persistent pain and opioid use in geriatrics: The thin line between love and hate

Pain is an unpleasant sensory and affective experience, that is the complex sum of injuries and sensory stimuli mediated by individual emotions and expectations. In accordance with the definition proposed by the Commission of Acute Pain in Elderly People of the American Geriatric Society, persistent pain is a pain lasting more than three months that may or may not have an evident causal disease process^[1].

There are several reasons why managing persistent non-cancer pain in older persons is a priority in health-care agenda. First, the prevalence of pain in older adults is high. Approximately 45%-85% of the older population complain about chronic pain in different settings^[2,3]. In particular, prevalence studies show that from 25% to 76% of older people living in community and from 85% to 93% of those living in residential care suffer from persistent pain^[4].

Musculoskeletal disorders are common in later life and osteoarthritis is the main cause of persistent pain in older adults^[5]. Other non-cancer causes include neuropathies, vertebral compression fractures, end-stage organ failures and stroke^[6].

Besides persistent pain is disabling in later life and high costly for healthcare^[7]. Chronic pain in older adults determines, through a multifactorial pathway, disabling condition, affecting proper ability to maintain independence and leading to a decline in social activities and isolation^[8]. Moreover relationship with mental distress, anxiety, depression, sleep disturbance and cognitive decline is well known^[9]. For all those reasons, we have to consider persistent pain in older people as a geriatric syndrome per se resulting in several sequelae (loss of mobility and independence, sarcopenia and decline in strength, inappetence, etc.).

Current approaches recommend that in older adults pharmacological interventions for persistent pain should be always part of a comprehensive and multidisciplinary approach (*i.e.*, psychological intervention, physical activity and complementary therapy); in this regard, opioid therapy should be considered in older patients with moderate-to-severe persistent pain or pain-related functional impairment or diminished quality of life due to pain.

As a matter of fact concerns about opioids use to treat chronic pain in older adults is present from both patients and providers side. Some old people believe that

using analgesic medication invariably results in adverse events and that long-term use is associated with an unacceptable high risk of addiction^[10]; the belief that chronic pain is a natural part of aging and it only could get worse over time^[11], and that any possible treatment is not likely to provide any meaningful benefit^[12]. Moreover, since older adults are more prone to drugs adverse events, clinicians sometimes are reluctant to prescribe opioids in this frail patients. Comorbidities and age-related changes in organ functions determine major concerns for opioids prescribing.

Nevertheless the rise in opioid prescribing - and consequent increasing risk of abuse, addiction, misuse or diversion - is actually a major concern in many countries, with reports coming from Australia^[13], United States^[14] and Norway^[15]. United States, Canada, Australia, and some Western European countries show very high levels of opioids use (over 43800 defined daily doses per million people per day in United States in the years 2011-2013), and in the period 2011-2013, use in North America increased in absolute terms from about 2.4 billion to about 5.3 billion defined daily doses per annum^[16], thus justifying more stringent strategies to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, reducing the risks associated with long-term opioid therapy^[17].

DISCOVERING OPIOIDS

What are opioids?

Opioids are a group of compounds that act by binding to opioid receptors which are distributed in the brain, spinal chord and periferal tissues. In general opioids are rapidly absorbed in the gut, have a high rate of first pass in the liver, are conjugated in the liver, have metabolites and vary in distribution based on their specific protein affinity, and are finally excreted through gastrointestinal or urinary tract. Opioids can act as agonists, antagonists and partial agonists/antagonists at peripheral and central opioid receptors. Fentanyl, hydromorphone, methadone, morphine and oxycodone are opioid agonists and buprenorphine is a partial agonist/antagonist. Tapentadol has a multiple mechanism, acting as an opioid agonist and noradrenalin and serotonin reuptake inhibitor^[18].

Opioids are the most powerful pain reliever-drugs and in general opioid prescribing is supposed to respond to the clinical needs of older adults who require effective relief from moderate-to-severe persistent pain.

OPIOIDS USE AND OLDER ADULTS

Opioids and age-related organs functions' changes

Organs functions progressively decline with aging. The age-related changes in drug metabolism occurring in the old population shall be considered. Aging decreases hepatic blood flow and volume, which influence opioids metabolism^[19]; opioids clearance can be also altered because of age-related reduction in renal blood flow and

glomerular filtration rate (GFR)^[20]. For those opioids with a primary renal clearance - such as morphine, tapentadol and hydromorphone - decrease in GFR could lead to more side effects. Thereby an estimation of creatinine clearance and hepatic function is always needed to guide clinicians in dosage adjustments.

Common geriatric conditions, like malnutrition, under-weight and sarcopenia, can lower serum albumen concentration, thus increasing the free fraction of opioids which are protein-bound; it prompts to potentially increasing side effects.

Of note, in geriatric patients the chronic - and highly prevalent - use of proton pump inhibitors H₂-receptor antagonist could alter drug absorption by increasing gastric environment pH^[21].

Polypharmacy and comorbidities: Never forget them in the elderly

Persistent pain in older patients often occurs in the setting of multiple comorbidities and it limits treatment options. In fact, elderly people suffer from several chronic conditions^[22] and they often are under polypharmacy. The attendant risk of drug-drug interactions increases exponentially with the number of medication taken^[23]. Moreover drug interactions are likely to increase by the consumption of over-the-counter (OTC) medications, which patients often perceive to be not important, tending to omit to their physicians^[24]. Interactions between drugs can lead to either serious adverse events or a reduction in therapeutic effect. Thus, it is fundamental to be aware of all the medications that the patient is taking, including OTC drugs, and the doses of each preparation.

CURRENT APPROACHES TO PAIN MANAGEMENT IN OLDER ADULTS: THE ROLE OF OPIOIDS

When managing persistent non-cancer pain in older adults, clinicians are supported by recommendations provided by national guidelines^[25] - those by American Geriatric Society (AGS)^[26] and British Geriatric Society (BGS)^[4] are the best known - and several consensus statements^[27-29].

Both AGS and BGS guidelines recommend to consider rarely and with extreme caution anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors use in older adults with persistent pain, owing to risk of gastrointestinal bleeding^[30] - which increases in frequency with age^[31] - cardiovascular and kidney dysfunction^[32,33]. Thereby all patients taking NSAIDs should be assessed for gastrointestinal and renal toxicity, hypertension, heart failure and potential drug-drug interactions; in general short-term NSAIDs use at low effective dosage is allowed in the old population^[4,26].

Acetaminophen is recommended for mild-to-moderate pain of musculoskeletal origin^[25-27], even though limited effectiveness of acetaminophen compared to

placebo and other analgesics has been shown. In knee and hip osteoarthritis, as well as for the treatment of severe low back pain, acetaminophen does not seem to confer any demonstrable effect or benefit, irrespective of dose^[34].

Current guidelines recommend that opioid therapy should be considered for old patients with moderate-to-severe persistent pain, pain-related functional impairment or diminished quality of life due to pain^[25].

According to these guidelines a lower than normal 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^[4,25-27].

Despite authoritative indications, management of persistent pain in older adults still lacks in everyday practice. As example, a national Canadian study documented that only 7% of older adults with disabling moderate-to-severe pain were receiving opioids stronger than codeine^[35]. Of note, older people commonly use OTC analgesics and 40% of them do not experience any relief from pain from these medications^[10]. In this regard, around the clock pain control vs "on demand" methods are preferable^[21].

However we should not forget what's so relevant when treating persistent pain, especially in older adults: opioid therapy - and in general any pharmacological treatment - is likely to be more effective when it is part of a comprehensive and multidisciplinary approach (e.g., psychological intervention, physical activity and complementary therapy); in fact relevant studies show that older people generally feel more comfortable with a multimodal treatment approach.

ARE OPIOIDS FOR CHRONIC-NON-CANCER PAIN EFFECTIVE IN OLDER ADULTS? CLINICAL EVIDENCE BETWEEN MYTH AND REALITY

Theoretically, all opioids may be suitable for older and frail adults; however because of inter-patient variability, opioid rotation or switching may result in better tolerability and efficacy for some patients.

A meta-analysis by Furlan *et al*^[36] stated that opioids have better outcome than placebo in reducing pain and improving functional activities, as well as being more effective for both nociceptive and neuropathic pain^[37]. In 2010 a meta-analysis of 43 treatment studies examining the effects of opioid-use among older adults mostly suffering from musculoskeletal pain demonstrated positive effect sizes for reductions in pain and physical disability, but not for improvement in quality^[38].

Evidence from trials show that opioid therapy for geriatric patients can be safe and effective with appropriate cautions, including lower starting doses, slower titration, longer dosing interval and more frequent moni-

toring^[4]. As example, in a large population ($n = 13179$ patients) transdermal buprenorphine proved to be effective and well tolerated in the treatment of chronic pain, irrespective of the patient's age^[39].

Even though the belief that neuropathic pain (which accounts for many chronic intractable conditions) is not responsive to opioids, opioid analgesics are recommended as generally second-line treatments in neuralgia; remarkably they also can be considered for first-line use in select clinical circumstances, such as severe or acute pain^[40]. Moreover, combination analgesic therapy with opioids and anticonvulsants has been shown effective for treating neuropathic pain^[41]. In particular, the combination treatment with morphine or oxycodone, and gabapentin or pre-gabalin resulted in a greater reduction in pain than did anticonvulsants or opioids alone, with beneficial effects on mood, pain-related interference with daily activities, and quality of life: Of note especially in geriatrics, these results were yielded with lower doses of each medication than each did alone^[42].

Long-term opioids use generally raises concerns in clinicians because of inconsistent clear positive risk-benefit-ratio. A recent 52-wk extension phase-open-label study showed that prolonged-release oxycodone-naloxone achieved satisfying analgesic effect in older adults (mean age 81.7 years) in absence of major adverse events or addiction^[43]. A prolonged longitudinal study among nursing home residents ($n = 10372$) with persistent pain revealed that long-acting opioids use may be a relatively safe option in the elderly population, yielding benefits in functional status and social engagements^[44].

However taking medications to reduce pain should be part of a global approach to pain in older adults. Being involved in physical activity and participating into programmes that aim at improving social and psychological functioning are essential. Only in this regard, appropriate opioids use may synergistically allow old patients to achieve their goals.

IS PRESCRIBING OPIOID SAFE IN FRAIL OLDER ADULTS?

Although there aren't generally absolute contraindications to opioid use for managing chronic non-cancer pain in older adults, caution is needed to minimize side effects and risks, in particular in those with several comorbidities and polypharmacy.

Opioids have side effects that could be prevented and are manageable with some cautions. In older adults opioids-related adverse effects could differ from those in younger patients, in particular for clinical relevance as schematically described below. Constipation: The most common adverse effect of opioid therapy. It is experienced by around 40% of patients taking opioids for chronic non-cancer pain. Contrary to other adverse effects, tolerance to opioid-induced constipation (OIC) does not develop. To prevent or reduce opioid-

induced bowel dysfunction laxatives should be initiated preventively at the same time when an opioid therapy is started^[16]. Alternatively, prolonged-release formulation of oxycodone/naloxone is a suitable approach in older adults to prevent OIC^[4]. Due to its very low systemic bioavailability, it predominantly antagonizes opioid receptors in the gastrointestinal tract, thereby preventing bowel dysfunction^[45,46]. Nausea: It is among the most frequently reported adverse events during opioid therapy^[47]. It occurs at the beginning of the treatment and it can be prevented by slower titration to the effective dosage and, if needed, antiemetics. Central nervous system (CNS): Sedation is another common adverse effect associated with opioid use in the elderly. It generally occurs at the beginning of an opioid trial and disappears after a few days^[48]. Combinations of opioids and CNS depressant drugs - such as antipsychotics or benzodiazepines - may have an additive role in sedation and it should be avoided. Mental confusion and hallucinations could appear in older adults during opioid therapy; these adverse events were reported less frequently in oxycodone group than in the morphine group^[49]. Of note, observational studies revealed that opioids do not influence cognitive functions in elderly patients^[44,47]. Delirium: In older adults opioids are associated with an increased risk of delirium; in the case of opioid therapy caution should be tempered with the observation that untreated severe pain can itself cause delirium^[50]. Low-doses and slow titration may prevent older adults from developing delirium. Falls and fractures: Opioids use has been associated with a substantially increased risk of falls and hip fractures in geriatric patients^[51]. Clinicians should be aware that this risk is dose-dependent and higher for short-acting opioids than long-acting opioids, especially during the first two weeks of therapy^[52]. It is generally believed that fracture-risk results from dizziness and sedation leading to falls, but some researchers suggested that opioids might also interfere with bone formation through suppression of endogenous sexual hormones production. Respiratory depression: It is rare with long-term treatment and occur with dosing changes, errors or misuse. Respiratory depression doesn't occur if low drug-doses and slow titration are used during treatment initiation. Immunosuppression: Opioid-induced immunosuppression is a phenomenon mediated by the presence of μ -opioid receptors in immune cells in the CNS. Morphine and fentanyl appear to have higher immunosuppressive effects^[53]. Selection of an opioid drug for long-term treatment should consider this effect in the older adults. Overdose: The recent marked increase of opioid overdose cases in the United States and Northern Europe is a major concern. Inadvertent overdose could be common in older patients, often related to insufficient care-giver support and practitioner expertise with rapid dose titration and failure to appreciate the inter-individual variability in dose requirements and response. Other potential causes of overdose in the elderly include concurrent use of alcohol, inadequately treated pain and

Table 1 Management of opioid-related adverse effects in older adults

Adverse effect	Frequency	Management
Constipation	+++	Prescribe laxatives when starting opioids Consider oxycodone/naloxone preparation
Nausea	+++	Low doses and slow titration To treat with antiemetics
Sedation, mental confusion	+	Careful review of medications (benzodiazepines, antidepressants, etc.) Low doses and slow titration
Delirium	+	Careful review of medications (benzodiazepines, antidepressants, etc.) Low doses and slow titration
Falls, fractures	+/-	To monitor walking instability and fall risk when initiating opioids Careful review of medications To prefer long-acting opioids
Respiratory depression	Very rare	Low doses and slow titration
Immunosuppression	Rare	To consider in long-term therapy
Addiction	Very rare	Abuse history Use tools to assess risk Monitoring patient

depression, particularly when compounded by awareness of dismal prognosis and hopelessness^[54]. Addiction: Risk of addiction is possible in the elderly but it is lower than in middle-aged patients^[55]. Clinicians should ask all patients about any substance abuse history. Screening questionnaires can be helpful in determining a patient's risk of opioid misuse and addiction. As example, the Opioid Risk Tool is the simplest and most widely used of the screening tools^[56].

Higher rates of adverse effects are observed with initiation of opioids, but data also suggest that these may be preventable if monitored closely. Few available studies on prolonged opioids therapy in older adults find no significant incidence of long-term adverse events^[45,46].

Common opioid-related adverse effects in older adults and their management are resumed in Table 1.

BRINGING EVIDENCE TO PRACTICE: PRESCRIBING OPIOIDS IN OLDER ADULTS

Existing guidelines for managing persistent pain in older adults recommend that opioid therapy for elderly patients can be safe and effective in patients with moderate-to-severe pain with appropriate cautions^[4,24-27]. Despite these recommendations nowadays in clinical practice NSAIDs continue to be one of the most commonly prescribed and consumed analgesic agents in the elderly^[57]. It is estimated that over 100000 hospitalizations occur annually on account of NSAIDs-induced gastrointestinal and renal toxicity^[58] and that approximately 20% of all congestive heart failure admissions can be attributed to NSAIDs use^[59]. NSAIDs prolonged-use is particularly hazardous in older adults with hypertension, peptic ulcer disease or impaired renal function.

When using opioids in older adults, some recommendations should be followed before, when and after prescribing them.

Before prescribing opioids: Proper assessment is essential

Older adults with persistent pain vary in their response to opioids and their risk of complications; assessment of concurrent medications, cognitive and behavioral status and social support should be encouraged before starting a opioid trial.

Before prescribing opioids in the oldest, some factors must be taken into account (Table 2): As physiologic changes due to aging could lead to altered drug metabolism, renal and hepatic functions assessment is fundamental; polypharmacy: Assessment of medications is essential in this population. Concurrent use of over-the-counter NSAIDs, benzodiazepines or other sedatives place patients at higher risk for morbidity or mortality^[60]; multimorbidity: Chronic conditions - such as disorders of gait and balance, kidney and cardiovascular diseases - should always be taken into account; tools to assess risk of addiction or abuse are strongly recommended; even though risk of opioids misuse/abuse is unfrequent in the elderly population, additional prescribing information and prescribing tools shall be regularly used in addressing any concerns about opioid risks and addiction^[31]; shared decision-making: Planning treatment and monitoring outcomes is recommended; it is important to establish realistic treatment goals, focusing on functional issues such as increased mobility or independence rather than pain intensity^[61]; drug prescribing for chronic pain in older adults should be part of a comprehensive management, that includes exercise and psychological interventions.

When prescribing opioids in older adults

When trialing an opioid treatment for an older patient the adage "start low and go slow" is recommended. Advise patients that treatment will start with a trial period of about four weeks. Opioids should be titrated slowly, using half the starting dose used for younger adults. A 3-d tolerance check is recommended after initiation or dose increase to assess for excess sedation or confusion^[25].

Staying too slow is unacceptable and could contribute

Table 2 Before prescribing opioid treatment in older adults

<p>Consider age-related physiological changes (creatinine clearance, hepatic function, serum albumen) Assess polypharmacy (over-the-counter analgesics, benzodiazepines, antidepressants, antipsychotic drugs) Consider multimorbidity Use tools to assess risk of addiction Share realistic treatment goals and make therapeutic plan Consider exercise and psychological interventions</p>

Table 3 When prescribing opioids in older adults

<p>Beginning at the lowest possible dose and titrating upwards base on tolerability and efficacy Longer dosing interval and regular monitoring are recommended Switching to another opioid might be indicated in cases of unacceptable side effects of insufficient analgesia The oral route may be the most convenient Low-doses of strong opioids should be preferred to weak opioids because of its effectiveness and safety Strong opioids generally recommended in frail old population are buprenorphine, hydromorphone and oxycodone (including oxycodone/naloxone formulation) Controlled-release formulation and transdermal formulations are generally preferred (low risk of addiction and adverse effects) Considering laxatives or oxycodone/naloxone to prevent constipation Over-the-counter analgesics use should be avoided</p>
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to under-treatment. In fact, if treatment goals are not met and the patient tolerates the therapy, advancing dose is reasonable before moving on to another intervention^[62]. Switching to another opioid might be indicated in cases of unacceptable side effects or insufficient analgesia.

The least invasive route of administration should be used; the oral route may be the most convenient and it can rapidly provide relatively steady blood concentrations; transdermal administration may be preferred in the context of opioid rotation or switching (paying attention to equivalent doses), or for uncompliant patients, and those unable to swallow, also to reduce staffing requirements in residential and nursing homes. Given the high potency of transdermal fentanyl, it should not be used for opioid initiation^[4]. Sudden opioids withdrawal should be avoided.

In general low-dose of strong opioids should be preferred to weak opioids (tramadol and codeine) because of its effectiveness and safety^[21,22]. Prescribing weak opioids could require higher dosage to reach adequate analgesia and high doses are likely to determine harmful adverse events in the old population.

Tramadol has a different mode of action to other opioids as it inhibits the neuronal reuptake of both norepinephrine and serotonin. Particular when used in combination with selective serotonin-reuptake inhibitors, tramadol has the potential to cause life-threatening events such as serotonin toxicity or serotonin syndrome. This is a clear limitation to tramadol use in the elderly because of the high concurrent rates of depression in this age-group. Furthermore, there should be recognition that there is individual variability in codeine's efficacy dependent upon drug metabolism into its active metabolites. Up to 30% of the population has been reported to be poor hydroxylators of debrisoquine required for codeine activation.

Buprenorphine, hydromorphone and oxycodone (in-

cluding oxycodone and naloxone formulation) are the strong opioids more studied in geriatric patients^[37,38,43,45]. Morphine instead should be use with extreme caution in older patients with renal impairment.

On the contrary, actually the evidence to support tapentadol still lacks in specific old population. True efficacy and side effects profiles of tapentadol in this age-group are largely unknown, especially for long-term use^[59,61-63]. However, as tapentadol does not undergo significant metabolism by cytochrome P-450 system, the potential for drug-drug interactions is supposed to be lower than other opioids.

Since OIC is the most frequent side effect, pro-phyllactive laxative therapy should be initiated in nearly all patients using opioids. A proper approach to reduce OIC in the frail elderly is the fixed-dose combination oxycodone/naloxone because of its peculiar biochemical profile^[43,45,46].

Finally in order to improve the convenience for elderly patients and avoid the risk of addiction, the controlled-release formulation and transdermal formulations are generally preferred^[63], whereas OTC analgesics use should be avoided (Table 3).

After prescribing opioids: Addiction and side effects monitoring

If an opioid trial is undertaken, it is important to closely monitor whether treatment goals are met or adverse effects occur (arranging regular phone contacts or visits during the initiation and dose titration phase of treatment). When monitoring older adults using opioids clinicians must ensure that patients is adhering to treatment plan. On each contact "the four As" - analgesia, activities of daily living, adverse events and aberrant drug taking - should be regularly evaluated. In particular, any signs of misuse, abuse or drug diversion have to be assessed and regularly

(at least every 3 mo) monitored.

CONCLUSION

Managing persistent pain in older adults is a complex task, as the relevant presence of multiple comorbidities, polypharmacy and physiological vulnerability in this age-group. Formulating an effective treatment plan for older adults with persistent pain requires a clear understanding of comorbidities and psycho-social situation. However, common opioid-related harms can be minimized with an individualized approach to opioid prescribing tailored to patients' health status and risk factors.

Given the established opioids use-related risks, the potential negative effects must always be weighed against the consequences of untreated or partially treated pain. In fact, the consequences of inadequately treated pain itself can determine impaired function, decreased independence in daily activities and depression.

Beginning at the lowest possible dose and titrating upwards base on tolerability and efficacy, longer dosing interval and frequent monitoring are strongly recommended^[4,24-27]. Prescribing opioids to older adults can be very gratifying when clinicians are adequately trained in pain management. Of note, even relatively low doses of strong opioids can be effective and safe; in our experience old subjects seem more prone to achieve therapeutic goals at low opioids-dosage than younger patients^[43,46]. This age-related feature is so remarkable as summarized by the adage "the lower effective opioids dose, the lower adverse effect".

In conclusion, when approaching an old patient with persistent pain the risk-benefit-ratio should address our approach to opioid-use, supported by recommendations from current guidelines and by evidence from clinical observations.

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