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REVIEW ARTICLE

Pharmacological Pain Treatment in Older Persons

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Abstract

Pharmacological pain treatment in older persons is presented by a multi-disciplinary group of European pain experts. Drugs recommended for acute or chronic nociceptive pain, also for neuropathic pain and the routes of administration of choice are the same as those prescribed for younger persons but comorbidities and polypharmacy in older persons increase the risk of adverse effects and drug interactions. Not all drugs are available or authorised in all European countries. For mild-to-moderate pain, non-opioids including paracetamol and non-steroidal anti-inflammatory drugs are first-line treatments, followed by nefopam and metamizole. Codeine, dihydrocodeine and tramadol are prescribed for moderate to severe pain and 'strong' opioids, including morphine, hydromorphone, oxycodone, fentanyl, buprenorphine, methadone and tapentadol, for severe pain. Chronic neuropathic pain treatment relies on coanalgesics, including anti-epileptics (gabapentinoids) and anti-depressants with additional option of topical lidocaine and capsaicine. The choice of analgesic(s) and the route of administration should be guided by the pain characteristics, as well as by the patient's comorbidities, organ function and medications. Several directions have been highlighted to optimise pharmacological pain management in older individuals: (1) before starting pain treatment adequately detect and assess pain and always perform a full geriatric assessment, (2) consider kidney function systematically to adjust the doses of analgesics and avoid the risks of overdose, (3) start with the lowest dose of an analgesic and increase it gradually under the control of the effect, (4) involve the older persons and family in their treatment, (5) reevaluate pain regularly during treatment and (6) combine pharmacological treatment with non-pharmacological approaches.

Key Points

The choice of analgesics in older individuals should be based on careful assessment of pain, taking into account patient condition, comorbidities and other medications.

Drugs should be started with lower doses, adjusted to patients' age, liver and renal function.

Careful titration is needed to achieve analgesic efficacy without side effects.

Treatment should be regularly evaluated for efficacy and safety.

Side effects must be quickly recognised, assessed and managed.

1 Introduction

Pain is very common in older persons: it is estimated that 40–75% of people living at home and up to 90% in care facilities suffer from chronic pain, and a global trend of rising pain prevalence in Europe and worldwide is observed [1–4]. Patients aged over 85 years are four times more likely to be admitted to emergency departments than patients aged 35–59 years and many of them have acute pain and cognitive impairment at admission [5, 6].

Pain is often under-estimated and under-treated in older people, in particular abdominal pain, low back pain and pain due to fractures or other trauma [6, 7]. Pain can be acute (< 1 month), subacute or chronic (> 3 months), nociceptive (such as a toothache), nociplastic (such as fibromyalgia) or neuropathic (such as post-herpetic or post-diabetic neuralgia). The use of regular prescribed analgesics, specifically paracetamol, in populations aged 75–95 years is reported to have increased over the last two decades, the use of non-steroidal anti-inflammatory drugs (NSAIDs) has decreased and daily opioid use has remained modest (2–3%)

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[8]. Although the range of available analgesic drugs and of non-pharmacological approaches to pain is the same as for younger patients, pain management in older people has a number of specific age-related features, including pain pathophysiology and assessment, and clinical pharmacology of many analgesics. Adverse effects, drug interactions and drug–disease interactions are more common. Polypharmacy in older age linked to multi-morbidity increased globally over the last 20 years, despite improvements in specialist geriatric care [9–11]. Chronic pain may lead to a deleterious cascade of impaired cognition, frailty, functional decline and loss of autonomy [12].

Consensus guidelines have been developed worldwide for pain detection and assessment in older persons, and expert consensus recommendations on pain treatment in older people have been published [13–19]. Synergy between pharmacological and non-pharmacological approaches are recommended [13, 15, 20]. However, most guidelines on pain management in older persons have been published at national levels, and there are so far no consensual recommendations involving clinicians working in different European countries. Guidelines are, however, needed as clinical care and drug availability and use may vary across Europe. This present position paper aims at focusing on a European context on the pharmacopeia used for pain alleviation and specifically addresses pharmacological pain treatment by European clinicians and experts focusing on pain management in older persons.

2 Methods

The development of this work employed a multi-faceted approach including a literature review to identify international and national guidelines, online panel of experts' discussions and consensus meetings. A scoping review (G.P. and M.K.) on current literature of international guidelines on drug approaches for pain management of older people, especially American, British and French recommendations, was carried out. The work is also based on the summaries of product characteristics (SPC) of analgesic medicines and on the opinion of experts in their field of pain management in different countries in Europe [13–18, 21, 22]. The panel (all co-authors) was selected on the basis of their clinical expertise in pain medicine, geriatric and palliative medicine, clinical pharmacology, medical oncology and pharmacy. The expert had at least 10 years of clinical/academic work in the field of pain and a record of international publications on geriatrics and/or pain management, and all played a crucial role to reach the present consensus. All experts belong to their own national Pain Society, to the European Pain Federation (EFIC) or to the International Association for the Study of Pain (IASP), and some are also members to the EFIC Geriatrics Task Force (G.P. lead). Online meetings and emails were held at various stages throughout the project to discuss, decide recommendations and handle disagreements.

3 Use of Analgesics in Older People

The choice of an optimal pain treatment is based on pain characteristics, past pain treatment, concomitant diseases, liver and renal function, drugs for comorbidities (to avoid drug–drug interactions), mental and psychological states, patient functioning and ability for self-care, ability to swallow tablets and support from the caregivers. Older patients with pain must always have a full geriatric assessment before starting a pharmacological pain treatment. The geriatric assessment in hospital [23] and in primary care [24] involves a multi-dimensional approach including comorbidities and drug intake. Concomitant diseases with all drugs taken on a regular basis or as rescues must be acknowledged. Pharmacotherapy needs to be limited to relevant and necessary drugs.

All pharmacological classes used in adults and traditionally classified as non-opioids and opioids, according to their main mechanism of action are used for pain management in older people [25, 26]. Coanalgesics, such as certain antidepressants and anti-epileptics, are prescribed for the management of neuropathic pain or nociplastic pain [27]. The availability of specific analgesic drugs and co-analgesics may vary across European countries. Non-opioid analgesics include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and, also, metamizole and nefopam, the two latter available in some countries only. So-called 'weak' or 'step 2 opioids' of the World Health Organisation (WHO) classification include codeine, dihydrocodeine and tramadol, used for the treatment of moderate to severe pain from the outset or for pain that does not respond to the use of non-opioids. In this class of drugs, there are specificities in some countries. For example, opium powder, 'step 2 opioid', is marketed only in France. Strong opioids are indicated for severe and very severe pain, as well as in moderate-to-severe pain that does not respond to step 2 opioids. Opioid switching, a therapeutic strategy of replacing one strong opioid, pharmaceutical formulation or route of administration with another to improve the benefit/risk ratio of pain treatment [28]. It is indicated in selected situations of insufficient pain control and when adverse effects cannot be easily controlled by symptomatic treatment. Nitrous oxide may be an option for the prevention of procedural pain and is used in some countries for painful pressure ulcers and wound care [29] in combination with other analgesic treatments.

Table 1 summarises recommendations of the expert group regarding optimal use of analgesics for older persons, and Table 2 presents general principles for the use of opioid

Table 1 Analgesics recommendations of the expert group for older persons

Drug	Indication	Recommended dose (IR, immediate release; PR prolonged release, PO, oral; TD,transdermal; SL,sublingual;TM transmucosal)	Use in hepatic impairment (HI) and renal impairment (RI)	Supplementary remarks
Non-opioids				
Paracetamol	Mild-moderate pain	PO: 300–500 mg every 4 h or 500–1000 mg every 6 h Maximum daily dose 2–3 g/day	2 g/day	
Ibuprofen		PO: 200 mg every 8 h	CI	Use for the shortest time if no other option
Diclofenac		PO: 50 mg every 12 h	CI	Use for the shortest time if no other option Due to relative selectivity to COX2 may be associated with higher cardiovascular risk compared to other traditional NSDAIDs
Meloxicam		PO 7.5 mg/day		
Celecoxib		PO: 100–200 mg/day		
Metamizole		PO: 500 mg every 6–8 h		Bioavailability increases 2- to 3-fold
Opioids				
Tramadol	Moderate-severe pain	Starting dose PO IR/SC: 12.5–25 mg every 4–8 h; PO PR: 50–100 mg every 12 h. Patients ≤ 75 yo maximum 400 mg/day; > 75 yo elimination may be prolonged. The dosage interval should be extended if necessary, maximum 300 mg/day	Elimination delayed in HI and RI. Reduce dose and adjust intervals between doses if needed. If severe RI: maximum dose: 200 mg/day	In poor metabolizers of CYP2D6, analgesia is diminished. In ultrarapid metabolizers clinical effect is enhanced (increased risk of adverse effects)
Codeine		PO: 15–30 mg every 4–8 h	Use with caution in renal impairment; active metabolite (morphine derivatives) may accumulate	
Dihydrocodeine		PO: 15–30 mg every 6–8 h; PO SR: 60–90 mg every 12 h	Use with caution -Use low dose	
Morphine	Severe pain	Starting doses : PO IR: 2.5–5 mg every 4–8 h; PO SR: 10 mg every 12 h; SC: 1/3 of PO dose	Reduction of initial dose by 25–75% in HI and RI. In patients with RI : accumulation of active metabolites. Avoid in patients with severe HI and RI. In RI consider switch to an alternative opioid	
Oxycodone		Starting doses: PO IR: 2.5–5 mg every 4–6 h; PO PR: 5 mg every 12 h	Reduction of initial dose by 33–50% in HI and RI. Use with caution in HI and RI	PR oral formulation may last for 8 h. Shorten the interval between doses if needed
Hydromorphone		Starting dose: PO SR 1–1.3 mg every 4–6 h	Reduction of initial dose by 50–75% in HI and RI. Use with caution in HI and RI	
Fentanyl		TD: Titrate requirement for opioids using an IR oral preparation of an opioid and switch for transdermal patch if indicated. Usual starting dose: 6–12 µg/h. Increase dose if needed with intervals of 6 or more days monitoring closely. TM : only used in opioid-tolerant adult patients with cancer: start with 50–100 µg	Reduction of initial dose by 50% in HI and RI. Use with caution HI and RI	

Table 1 (continued)

Drug	Indication	Recommended dose (IR, immediate release; PR prolonged release, PO, oral; TD,transdermal; SL,sublingual;TM transmucosal)	Use in hepatic impairment (HI) and renal impairment (RI)	Supplementary remarks
Buprenorphine		Low initial doses and slow titration are recommended. Starting doses: SL: 0.2 mg every 8 h. Titrate if needed to 0.4 mg every 8 hours. TD: 5–17 µg/h every 3–7 days Increase dose with intervals of > 6 to 8 days to a maximum of 140 µg/h if needed.	Reduction of initial dose by 25–50% in HI and RI. Use with caution in HI and RI	
Tapentadol		Starting dose : PO IR: 50 mg every 4–6 h. Maximum recommended dose in adults: 500–600 mg/day (no specific recommendations for elderly)	Not recommended in severe HI and RI; starting dose in moderate HI: 50 mg every 8–12 h (IR) or once daily (ER)	
Coanalgesics				
Gabapentin	Neuropathic pain	Dosage adjustment . Starting dose: PO: 100 mg at bedtime. Titrate slowly every 3–7 days if needed. maintenance daily dose in divided doses every 8 h	Dose adjustment in RI and dialysis. No dose adjustment in HI	Almost exclusively eliminated unchanged by renal excretion
Pregabalin		Dosage adjustment: PO: start with a dose of 25 mg at bedtime. Titrate slowly every 3–7 days if needed. Maintenance daily dose in divided doses every 12 h	Dose adjustment in RI and dialysis. No dose adjustment in HI	Almost exclusively eliminated unchanged by renal excretion
Tricyclic antidepressants (amitriptyline)		Usually not recommended Starting dose: 10 mg et bedtime Use low doses	CI in cardiac disorders	Risk of cardioascular and anticholinergic adverse effects
Duloxetine		PO: start with 20–30 mg per day. Increase the dose after 1 week or more if needed. Titrate up to maximum 60 mg/day	CI in HI and RI. CI in uncontrolled hypertension	Avoid CYP1A2 inhibitors => may increase duloxetine serum concentration

analgesics. All recommendations were first derived from the expert panel and were in adequation with the literature review. The panel's decision was stronger than described in literature on the usefulness of topical patches and of NSAIDs; these should be used if necessary and with stringent conditions, along with metamizole, but this is not commercialised in all European countries. All recommendations are consistent with previously published expert consensus recommendations.

3.1 Non-opioid Analgesics

3.1.1 Paracetamol

Paracetamol has been widely used because of its noteworthy efficacy/tolerance ratio. It is recommended as a first-line treatment for mild-to-moderate acute and chronic pain in older people of various origin and pathophysiology, including joint and back pain which prevalence is very high in this population [8]. Recommended maximum oral doses in older persons vary according to countries, from 2 to 3 g a day. Post-operatively and in very old or frail patients, a dose adjustment according to weight is necessary: in malnourished patients weighing < 50 kg, the maximum recommended dose is 2 g/day [30, 31].

Paracetamol is an over-the-counter (OTC) medication, widely available in many preparations, including compound tablets with weak opioids, which raises risk of its duplication and overdose. The physician must pay attention to this aspect on treatment assessment.

Controlled studies and meta-analyses have, however, cast a doubt on the efficacy of paracetamol with regard to acute and chronic pain (e.g. low back pain, osteoarthritis and cancer) [32–35], as well as its tolerance [36–39]. For example, in post-operative pain management, it has been shown that only 36% of patients have ongoing pain relief over 4 h post-surgery as compared with persons who received placebo [39]. Nevertheless, clinical practice shows that paracetamol is effective in situations of mild-to-moderate pain, and it is relatively safe when compared with NSAIDs and opioids.

Reports of adverse reactions are uncommon; however, their prevalence is higher in older as compared with younger persons [40]. Acute overdose can occasionally lead to hepatotoxicity or even irreversible hepatic necrosis. In case of overdose, *N*-acetyl-cysteine, the antidote to paracetamol, has to be administered as soon as possible (the best effect is obtained up to 8 h after ingestion). Nevertheless, adverse hepatic effects have also been reported when taken at therapeutic doses [41–43], in particular, when the hepatic glutathione level is reduced in circumstances such as malnutrition, starvation, prolonged fasting, dehydration, cachexia, alcoholism, renal and hepatic insufficiency, post-surgery and in the concomitant use of certain anti-epileptics. Paracetamol should, therefore, be administered with caution, with a maximum dose of 2 g/day.

An adverse reaction to long-term regular use of paracetamol concerns its drug–drug interaction with warfarin and acenocoumarol, as paracetamol may increase its anti-coagulant effect [44]. Paracetamol should not be used concomitantly with carbamazepine, phenytoin, rifampicin, St John's Wort and other drugs that induce liver enzymes, because they may diminish the effect of paracetamol and increase the risk of liver damage due to increased production of toxic paracetamol metabolites. Fatal hepatotoxicity was observed in patients treated with paracetamol and tyrosine kinase inhibitors (imatinib and sunitinib) [45, 46], and with severe renal impairment [47]. Chronic use of paracetamol at 2–3 g/day together with systemic NSAIDs may result in increased risk of gastrointestinal (GI) complications and hospitalisation [38].

The use of paracetamol in mild-to-moderate pain remains also the standard in emergency departments and other settings such as palliative care. Intravenous (IV) infusions (on 15 min) are an efficacious alternative to the oral route. The peak serum concentration and time to maximum effect is more rapid with IV than after with oral administration, and efficacy is similar. It is advisable, however, to switch to oral administration of paracetamol as soon as possible [48].

Recommendations in acute and chronic pain

Table 2 General principles on the use of opioid analgesics in older persons

1. To improve tolerance, start with a low dose of an opioid and titrate slowly according to individual response
2. Decrease an initial adult dose of opioids by about 25% for individuals > 60 years old and by 50% for patients > 80 years
3. Initiate gradually one new analgesic or co-analgesic to improve tolerance and safety (most of these drugs exert central nervous system depressant adverse effects)
4. Increase dose of analgesics slowly by no more than 25–30% when required.
5. Advise patients on how to prevent and treat opioid-induced constipation and nausea/vomiting. Prescribe laxatives, including osmotic agents and anti-emetics if needed
6. Provide patients with written instructions concerning how to administer drugs, assess analgesia and adverse effects. Instruct patients as to whom to contact if necessary

- Paracetamol is indicated to be used as a first-line option in older patients with mild-to-moderate pain of nociceptive origin.
- Paracetamol alone is not recommended in neuropathic and nociplastic pain.
- Recommended maximum oral paracetamol dose for older people is 2–3 g per day.
- Dosage adjustment to 2 g per day maximum is necessary in individuals in the context of weight below 50 kg, factors that lead to glutathione depletion, severe renal and liver insufficiency, comorbidities or co-prescription of vitamin K antagonist drugs.
- It is important to ensure that the treatment is well understood by the patients, with respect to paracetamol taken erroneously as generics in different preparations and in self-medication.

3.1.2 Nefopam and Metamizole

Both drugs are non-opioids and not marketed, used or authorised in some European countries. Nefopam is a non-opioid centrally acting analgesic, mainly used in post-operative care and in emergency departments. It is not recommended for older patients due to the risk of disorientation and hallucinations [49]. It is contraindicated in patients with a history of seizures, severe renal or hepatic insufficiency, heart rhythm disorders or angina and taking monoamineoxydase inhibitors (MAOI), up to 3 weeks after their withdrawal [50]. Because of its anti-cholinergic activity and potential additive effect with anti-cholinergics and sympathicomimetics, it should be used with caution in patients at risk of or presenting with acute urine retention or angle closure glaucoma. It can cause tachycardia, nausea, dizziness, confusion, agitation, hallucinations, insomnia, headaches and others.

Metamizole (Dipyrone) is a popular analgesic, antipyretic and centrally acting spasmolytic agent, used for many acute and chronic pain conditions (postoperative, cancer and colic) and fever [51, 52]. It is a pro-drug that, after oral administration, breaks down to structurally related pyrazolone compounds. It can also be administered IV and used concomitantly with non-opioids (paracetamol and NSAIDs) and opioids, demonstrating additive or synergistic effect [53]. Several mechanisms of action have been proposed, including the involvement of the endogenous opioid system, inhibition of peripheral and central cyclooxygenases and inhibition of the activation of microglia [54–58]. The recommended parenteral or oral single dose in adults and adolescents aged 15 years or over is 500–1000 mg. A single dose can be taken up to four times daily at intervals of 6–8 h leading to a maximum daily dose of 4000 mg. However, it is appropriate to allow, if necessary, a parenteral single dose of 2500 mg metamizole and a maximum daily dose of 5000 mg metamizole [59]. Metamizole is considered in some publications as a safer non-opioid analgesic compared with paracetamol and NSAIDs [60], but drug–drug interactions are of concern [61, 62]. For example, metamizole may decrease serum concentration of CYP2B6 and CYP3A4 substrates (methadone, oxycodone and fentanyl, among others) or enhance the anti-coagulant effect of vitamin K antagonists. It has been withdrawn in several western countries because of its side effects. Rare adverse events, such as agranulocytosis, allergic reactions, hypotension and deterioration of renal function, may occur. It appears to be equally safe for all age groups, including older persons [63]; however, the risk of fatal outcome of metamizole-induced agranulocytosis is higher in older persons, especially those receiving methotrexate concomitantly [64].

Recommendations in acute and chronic pain

- Nefopam is not recommended in older people.
- Metamizole is an analgesic that can be used for many nociceptive pain conditions in older people such as visceral pain. It can be used alone or in combination (synergistic effect with opioids).
- Treatment with metamizole must be carefully monitored because of its rare but potentially fatal adverse effects.

3.1.3 NSAIDs

NSAIDs (and paracetamol) are currently the most widely available therapeutic options for mild-to-moderate pain, including over the counter (OTC) medications [19]. NSAIDs are commonly prescribed medicines for inflammatory, musculoskeletal pain and headaches but diversely recommended and even contraindicated in different countries. This pharmacological class includes conventional NSAIDs and selective cyclo-oxygenase-2 (COX-2) inhibitors. NSAIDs inhibit the COX-1 and COX-2 isoforms that catalyse prostaglandin synthesis. Prostaglandins play an important homeostatic role in gastrointestinal, renal and cardiovascular function, and advancing age increases the risk of dysfunction in these organs and systems. The safety profile of NSAIDs depends on the affinity ratio for the two COX isoforms. The preferential action on COX-1 or on COX-2 increase the risk of gastrointestinal or cardiovascular complications, respectively [65–67]. The improved tolerance of selective COX-2 inhibitors compared with traditional NSAIDs has not been demonstrated in older persons.

NSAIDs used in acute and chronic pain treatment can be delivered by different routes of administration, including oral, IV, intramuscular, rectal and topical. Due to a high risk of adverse drug reactions and drug–drug interactions, NSAIDs should be prescribed with caution starting with low doses, carefully titrated and used in pain management for the shortest time (< 8 days). The maximum recommended doses of NSAIDs should not be exceeded and only one systemic

NSAID given at the time. Topical NSAIDs should be considered before oral NSAIDs [19] for osteoarthritis of the knee and hand because of the analgesic efficacy and lower risk of adverse effects because of low plasma concentrations [68] but should not be co-prescribed with systemic NSAIDs [40].

Systemic NSAIDs are more effective than paracetamol for inflammatory pain and are recommended in individuals with osteoarthritis when paracetamol combined with topical NSAIDs turned out to be ineffective [69–72]. They are also used in patients with cancer with bone pain due to primary or secondary metastases to the bones. Nevertheless, in older people, there is a high risk of potentially serious side-effects of systemic NSAIDs that lead to frequent hospitalisation [73, 74].

Specific adverse-effects of NSAIDs in older people include [65–67, 75, 76]:

1. An increase in the frequency of gastrointestinal disorders (ulceration, perforation and bleeding) and their severity, especially if an NSAID is co-administered with low-dose aspirin used for cardiovascular prevention), corticosteroids, oral anti-coagulants (vitamin K antagonists, direct-acting anti-coagulants [DOACs]), selective serotonin reuptake inhibitors (SSRIs), other drugs with anti-platelet properties and dietary supplements (garlic, ginseng and ginko). These effects may be reduced by the prescription of a proton pump inhibitor (PPI). According to the current Beers Criteria endorsed by American Geriatrics Society, PPI therapy for > 8 weeks should be avoided unless the latter is for high-risk patients (e.g. > 75 years old, taking systemic corticosteroids, anti-coagulants or anti-platelet agents and chronic NSAID use).
2. An exacerbation of congestive heart failure and higher blood pressure following renal vasoconstriction and increased tubular reabsorption of sodium. Some NSAIDs (ibuprofen) may also diminish the anti-thrombotic and cardioprotective effect of aspirin.
3. A risk of acute renal failure or the aggravation of pre-existing chronic renal failure, particularly in patients treated with diuretics or converting enzyme inhibitor (ACEIs) and angiotensin II receptor blockers (ARBs).
4. Confusion is often described in older people when exposed to NSAIDs (i.e. indomethacin).

The safety of NSAIDs was discussed in coronavirus disease 2019 (COVID-19) infection. After initial controversy as to whether NSAID use is safe in patients with COVID-19 infection, evidence seems to indicate no increased mortality [77–79]. An investigation in population-based setting showed substantial NSAIDs and opioid purchases on prescription for older adults. This suggests the need for more information and community-based education on analgesics contra-indications, safety and combined use of non-pharmacological approaches [80].

Recommendations in acute and chronic pain

- Prescription of NSAIDs should only be considered after failure of paracetamol and/or topical NSAIDs and used only for nociceptive and inflammatory pain, not recommended in neuropathic and nociplastic pain.
- The analgesic dose must be as low as possible, used over the shortest period of time.
- The administration of two NSAIDs or exceeding the maximum recommended effective doses must be avoided.
- NSAIDs should be avoided in severe renal impairment, current or previous peptic ulceration and bleeding, platelet dysfunction, severe heart failure, severe hepatic impairment and when taking drugs with anti-coagulant/anti-platelet activity.
- For people of high-risk groups (aged > 75 years, taking corticosteroids, anti-coagulants and anti-platelets or previous ulcer disease), with chronic NSAIDs use, administration of a proton pump inhibitor is essential.
- Regular assessment is necessary to ensure that the risk/benefit balance remains positive by looking for adverse effects and potentially harmful drug interactions.
- Topical NSAIDs may be a good therapeutic alternative in osteoarthritis of the knee and hand.
- It is not advisable to combine NSAIDs with drugs that are widely used for older people including anti-coagulants, anti-platelet drugs, SSRIs, diuretics and dietary supplements.
- It is important to ensure that NSAIDs treatment is well understood by the patient, in particular when using generic drugs, OTC drugs, dietary supplements and in self-medication.

3.2 Opioid Analgesics

All opioid analgesics (WHO step 2 and 3) share common mechanisms of action and potential adverse drug events profile [13, 14, 81–90].

3.2.1 Tramadol and Codeine

Tramadol, codeine and dihydrocodeine are prescribed in moderate to severe pain or when non-opioids have failed, for acute and chronic non-cancer and cancer pain [91–97].

Genetic variation in the expression of cytochrome P450 2D6 (CYP2D6), a pathway for metabolising tramadol and codeine to active metabolites with affinity for the μ-opioid receptor, determines a highly variable efficacy/tolerance ratio of both opioids [98, 99]. Numerous drug interactions with concomitant CYP2D6 inhibitors commonly prescribed in geriatric medicine (for example, some anti-depressants

and anti-emetics), may result in diminished analgesia or increased toxicity.

Prescribing opioids, including 'WHO step 2 opioids' to older patients warrants special care regarding adequate dosing. Dosage guidelines are often extrapolated from younger adults, and these may correspond to excessively high opioid dose equivalences (Table 1). Compliance variability, timeframe between two doses, presence of a caregiver for treatment and patient's degree of autonomy are important factors to consider. Specific rules for prescribing WHO step 2 opioids in older people should be followed: (1) reduction (compared with younger adults) in initial doses of immediate release preparations and increased intervals between doses; (2) maximal doses used for the general population are not usually achieved in older people due to less tolerance, when using fixed paracetamol/weak opioid combinations paracetamol doses must be acknowledged to avoid paracetamol overdose; and (3) adverse events, broadly similar to those of strong opioids and dose dependent, should be anticipated and/or prevented (i.e. nausea, constipation and urine retention).

3.2.1.1 Tramadol Tramadol has a dual mechanism of action that explains its efficacy against neuropathic and nociplastic/functional pain: transformation into an active metabolite *O*-desmethyltramadol with an agonist effect on μ-opioid receptors, and inhibition of the reuptake of serotonin and norepinephrine by the parent molecule. Due to its complex mechanism of action tramadol can be considered a first-line treatment for mixed pain (neuropathic and nociceptive) [100, 101], but combinations with anti-depressants that increase the risk of serotonin syndrome must be avoided.

Side-effects such as nausea, vomiting, constipation (however, usually less intense than with codeine and strong opioids), reduction in seizure threshold (with an increased risk of seizures) and higher incidence of confusion and of delirium are well documented in older persons [102]. Combination with other serotoninergic drugs (anti-depressants, particularly SSRIs or MAOI such as selegiline, linezolid, lithium and dextromethorphan) or strong CYP2D6 inhibitors (paroxetine and fluoxetine) should be avoided, as this increases the risk of falls and serotonin syndrome. In addition to serious neuropsychiatric and gastrointestinal adverse events, hepatic and metabolic effects have been reported. Hypoglycaemia, increased anti-coagulant effect and hyponatremia are now well recognised problems with tramadol [103–105]. Close monitoring of serum electrolytes and International Normalized Ratio (INR) are, therefore, essential during the initiation and dose escalation of tramadol therapy in older persons. Tramadol should be used with caution in persons with weak to moderate renal and liver impairment and avoided in individuals with severe renal and liver impairment.

While fixed dose tablets may not be adequate, the oral solution (sometimes presented as a paediatric formulation with 10 drops corresponding to 25 mg) allows better individualised oral titration, as recommended by experts [13, 106, 107]. Titration should start between 12.5 mg and 25 mg every 4–8 h, depending on age, weight and kidney function. The progressive increase in tramadol dose should occur every 48–72 h, as needed. Good tolerance of tramadol allows a switch to the lowest sustained release form, while allowing additional doses of oral solution (10–20% of daily dose) to be taken up to three times a day if needed. The use of the oral solution at home may be limited in older people with cognitive impairment because of the need to precisely measure the dose to be helped by a caregiver. It is, therefore, essential to ensure that it is dispensed safely. The injectable form of tramadol also makes possible to administer tramadol subcutaneously as injections or by pump. The equivalence between oral and injectable dosages is not well known, but in practice, oral titration and maintenance therapy are applicable to the injectable form of tramadol.

In patients aged 75 years or older, the pharmacokinetics of tramadol changes [108], the bioavailability of *O*-desmethyl-tramadol (but not tramadol) increases by 35% compared with patients under 40 years of age and its elimination half-life doubles [109]. Therefore, for safety reasons, it is recommended that dosing of tramadol in older people should be adapted to renal function and not exceed a maximum dose of 300 mg per day from the age of 75 years or 200 mg in co-morbid patients [110]. Tramadol is also used combined to paracetamol to improve analgesia and avoid escalation of tramadol doses, thus limiting tramadol induced side effects [111–113]. Finally, tramadol is commercialised in fixed combinations with dexketoprofen in some countries [114]. Limited data are available in patients over 75 years, and fixed dose combination of tramadol 75 mg + dexketoprofen 25 mg should be used with caution in these patients, because of the increased frequency of adverse reactions to NSAIDs in older patients.

3.2.1.2 Codeine and Dihydrocodeine Codeine is used both for pain and cough and its analgesic activity is associated to its metabolism via CYP2D6 to morphine (5–10% of dose). In Caucasian populations, 8–10% of people are poor metabolisers; however, 3–5% are ultrarapid metabolisers [115]. Those who are ultrarapid metabolisers (carriers of the CYP2D6 gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine [116]. Its anti-tussive effect should be acknowledged, particularly in chronic lung disease frequently encountered in older people.

In practice, the multiplicity of formulations containing both codeine and paracetamol with variable dosages stresses that particular attention must be paid to prescribing,

specifying the desired dose of codeine. The lowest available dose varies according to countries (8 mg in Ireland and the United Kingdom and 20 mg or less in other countries). A dose of 16–20 mg codeine, taken every 4–8 h, is usually the initial dose in older people; it is commonly combined with 500 mg of paracetamol. The dosage can be increased to 30 mg of codeine per dose, bearing in mind that the maximum dose is 180 mg per day (240 mg/day in the United Kingdom). The effectiveness of codeine in the treatment of pain in older persons has been shown [117]. The sustained release form of dihydrocodeine is a worthwhile alternative to repeated codeine dosages after titration.

Dihydrocodeine (DHC) is a semi-synthetic analogue of codeine, used as an analgesic and anti-tussive agent and for the management of dyspnoea and opioid addiction. Limited data are available on the potency of DHC compared with other opioids. The analgesic effect of DHC is similar to codeine and approximately twice as potent as tramadol for an oral route. In contrast to codeine and tramadol, DHC analgesia seems to be irrespective of CYP2D6 activity [118]. The sustained release form of dihydrocodeine is an interesting alternative to repeated codeine and DHC intakes after titration. The usual starting dose of DHC sustained release is 60 mg every 12 h and may be increased to a maximum of 120 mg every 12 h.

Codeine and dihydrocodeine should not be used in patients with liver impairment due to unpredictable pharmacokinetics and used with caution in patients with renal insufficiency.

Recommendations

- Weak opioids have their place in the treatment of acute and chronic pain of moderate-to-severe intensity in older people.
- Tramadol is the drug of choice for mixed pain.
- Low starting doses of WHO step 2 opioids in older people, gradual increase and vigilance with careful monitoring of the therapeutic effect are recommended.
- Prescription of fixed paracetamol/weak opioid combinations must be rigorous and the dosage of paracetamol and of opioids carefully specified.
- Tramadol should be avoided patients taking other serotoninergic medications and in those with severe impaired hepatic and renal function.
- Step 2 opioids have significant side-effects and an addictive potential similar to strong opioids.

3.2.2 Strong Opioids

Prescription of strong opioids is not related to the severity of the disease but to the intensity of pain and impact on the patient's functioning and quality of life. Traditionally associated with the treatment of cancer pain or acute, post-operative and post-traumatic pain, most strong opioids now have also marketing authorisation in chronic non-cancer pain. Principles that rule the treatment of pain in general adult population are extrapolated to aging because of the paucity of data available in older people. The choice of a specific opioid should be based on the known pharmacology characteristics, as well as the convenient route of administration and the available formulations. The dose of opioids should be adjusted according to the analgesic effect and the severity of side effects. There is no maximum dose of strong opioids that should not be exceeded due to age; although, there is no evidence that high doses are more effective than lower doses and to dose-related harms, including overdose and death. When guidelines for use in older people are complied with, strong opioids may be easier to use and with less adverse events than weak opioids or NSAIDs [81, 82, 88]. In general, the risk of addiction is very low and lower than in younger people (1–3% of older adults demonstrate opioid abuse or dependence) [119]. The literature search demonstrates a limited evidence for the use of opioids in cancer and non-cancer pain (low back pain and osteoarthritis) particularly in long-term use and older patients [117].

3.2.2.1 Morphine Morphine is a pure mu-opioid receptor agonist. The age effect results in a higher circulating blood concentration of the parent drug and active metabolites and slower elimination in older people compared with younger people at the same dose. It is, therefore, necessary to adjust the dose of morphine by titration of small doses of sustained-release morphine (10–20 mg/day) for a baseline dose and immediate-release morphine for acute exacerbations. Alternatively, immediate release preparations can be administered regularly every 4–8 h (starting with 2.5 mg), with additional doses as required. Doses need to be lower and intervals between doses adjusted in patients with renal impairment due to the risk of accumulation of active morphine metabolites (morphine-6-glucuronides and morphine-3-glucuronides, the latter having neurotoxic properties).

IV morphine is used to relieve acute pain or severe exacerbation of chronic pain in emergency units and in in-patient settings. Titration needs to be cautious with subsequent boluses of 1–2 mg administered every 10–15 min. Subcutaneous (SC) morphine is an alternative used mostly in palliative care patients with difficulty swallowing. Due to low bioavailability of oral morphine, SC doses need to be reduced to about a third of oral doses. Intervals between subsequent SC doses are 4–8 h, the latter when morphine elimination is slowed; SC continuous infusion may also be used.

Studies show good efficacy and relatively good tolerance of treatment with morphine in older patients. An international consensus statement and review [85] showed that older persons with chronic severe pain respond, as well as or even better, to morphine than younger age groups and

suggested the need to address the problems with under prescribing in older persons. It is important to ensure safe morphine prescribing in older persons with chronic kidney disease, a common comorbidity, as there is evidence that accumulation of active metabolites can lead to opioid toxicity [110], and caution is mandatory in the frail elderly [120].

Hydromorphone has pharmacokinetic properties comparable with those of morphine and is used mainly in the context of opioid rotation.

3.2.2.2 Oxycodone When given orally, this pure μ- and κ-opioid receptor agonist is 50% more potent than morphine. Its renal elimination justifies, as with morphine, a progressive dosage reduction in older people. Ten percent of oxycodone is converted by CYP2D6 to active oxymorphone that may accumulate when renal function is decreased. Initial doses of sustained release preparations administered twice daily in older people are recommended. Immediate release preparations can be used on a regular base or as rescues. Combined formulations of oxycodone and naloxone prolonged-release tablets are available for patients with opioid-induced constipation. These formulations need to be used with caution in older people and individuals with renal impairment and are contraindicated in moderate and severe hepatic impairment (due to the risk of the increased naloxone bioavailability and its potential antagonizing effect on opioid analgesia). Studies with oxycodone in older persons have been reviewed [117].

3.2.2.3 Fentanyl Fentanyl is a pure μ-opioid agonist used in acute (IV) and chronic pain management for baseline (transdermal formulation) and breakthrough pain (transmucosal formulations). Transdermal fentanyl is usually highly effective and less constipating than morphine and oxycodone. Due to high potency, its commencement and further titration need to be extremely cautious. Transdermal fentanyl is never recommended for initiating a strong opioid both in young and older people [4]. Its use should be proceeded with dose titration with immediate release opioid (usually morphine). Long delay in reaching a steady state does not make fentanyl a first-choice drug in the titration phase of analgesic treatment. The lowest dose patch (12 μg/h) is already equivalent to 30–45 mg/day oral morphine. Greater variations in the transcutaneous absorption in older persons makes it more difficult to anticipate its bioavailability [85]. Due to its high lipid solubility, fentanyl is eliminated more slowly in older people but is the opioid of choice in renal failure and for individuals on dialysis [110].

Transmucosal (buccal, sublingual and intranasal) fentanyl has a marketing authorisation for breakthrough pain in cancer in adults. Formulations with a very short onset of action (5–15 min) are useful in pain exacerbations, but prescribers should be aware that xerostomia, frequent in older people, can affect fentanyl absorption and effect. A strong consensus was achieved regarding which pharmacological treatment (transmucosal fentanyl) and dosing method (start low and go slow) are the most suitable for the older population suffering from breakthrough cancer pain [121].

3.2.2.4 Buprenorphine Buprenorphine is a partial agonist at μ-opioid receptor and a κ- and δ-opioid antagonist [122]. It is available in sublingual tablets and transdermal formulations but not authorised in all European countries in the context of pain. The recommended starting dose for non-cancer pain is 0.1–0.2 mg every 8 h in transmucosal tablets and 5–17 μg/h in transdermal patches (equivalent to approximately 10–30 mg of oral morphine per day). Buprenorphine is usually well tolerated, with lower respiratory depressant risk, and is less likely to cause cognitive impairment than other opioids [122–126]. It can also be recommended for renal impairment or in patients having dialysis [127]. In older persons, the risk of falls and subsequent fractures induced by opioids should be taken into clinical consideration, but buprenorphine presents a lower risk than tramadol and other strong opioids [117, 128, 129].

3.2.2.5 Methadone Methadone is a combined μ-opioid agonist and NMDA receptor antagonist, with a long and variable half-life (8.5–120 h) that makes it risky to introduce and dose adjust in older people, particularly in patients on dialysis. Due to the lack of active metabolites it can be used in people with renal impairment, including dialyzed patients [127]. It is a substrate of CYP450 (mainly CYP2B6 and CYP3A4), susceptible to drug interactions when combined with inhibitors or inducers of the metabolizing enzymes [130]. The possibility of prolonged QT interval with potentially serious ventricular dysrhythmias is significant and requires regular cardiac assessment (ECG and electrolytes level) [131]. It is mainly used in palliative care and reserved for physicians experienced in pain management.

3.2.2.6 Tapentadol Tapentadol is a synthetic opioid, not available in all European countries, with a dual mechanism of action of μ-opioid receptor agonism and noradrenaline reuptake inhibition. It has a low risk of drug interactions, due to reduced plasma protein binding, predominant metabolism by glucuronidation and lack of impact on CYP450 enzymes [132, 133]. It is effective and well tolerated in older patients suffering from musculoskeletal pain, but because of limited data, there is insufficient evidence to support the use of tapentadol over other opioids [134, 135].

3.2.2.7 Nalbuphine Nalbuphine is a μ-opioid receptor antagonist and κ-opioid agonist. It is available in injectable formulation only and used post-operatively or in emergency departments for acute pain but never in chronic pain due

to its antagonist action at μ-opioid receptors. Nalbuphine requires hepatic metabolism and renal elimination; it is necessary to adjust dosage to impaired liver and kidney function. The evidence of nalbuphine in older patients is very sparse. Single studies showed, that in intensive care pain management, in patients over the age of 60, nalbuphine has worse analgesia than sufentanil [136]. The authors recommend that because of altered pharmacokinetics and clearance in older, debilitated or cachectic patients, caution should be used when administering nalbuphine to these patients because life-threatening respiratory depression can result [137].

3.2.3 Side Effects and Drug Interactions of Opioid

3.2.3.1 Side Effects Side effects are similar in older people as in younger adults, and their incidence is limited by applying best practice guidelines for older persons. Constipation is common [138] and often already present before the opioid is prescribed. Laxatives acting through different mechanisms (starting preferably with osmotic agents, e.g. lactulose or macrogols) should be used or increased as soon as the opioid is introduced in addition to the recommendations for diet and hydration. Use of oxycodone/naloxone preparations may be considered in some patients. Bowel function in patients on chronic opioid therapy need to be closely monitored. Nausea and vomiting may occur with an initiation of an opioid but usually disappear after a few days of regular daily treatment. Nausea may be relieved for example by low doses of metoclopramide or haloperidol. Care must be taken to prevent dehydration, as older people may not always feel thirsty due to lower age-associated osmoreceptor sensitivity and, consequently, may not drink sufficiently. Drowsiness, often increased by the co-prescription of other potentially sedative drugs (benzodiazepines, hypnotics such as zolpidem, zopiclone and zaleplon), requires an adjustment of opioid dosage. If it appears during treatment, kidney function should be checked. Urinary retention is more likely if the patient has marked constipation or prostatic hyperplasia. Confusion linked to opioids must be well documented as urinary retention, electrolyte/metabolic disorders, dehydration, inappropriate sedative or psychotropic medication and unrelieved pain may also be a cause of confusion. Falls and fractures are a major concern as evidence indicates that older patients using opioids are at higher risk of falls and fractures, with a highest risk in the first two weeks after opioid initiation. Closer monitoring particularly in the first weeks of opioid therapy and education of the patient's family need to be undertaken [139, 140].

3.2.3.2 Drug Interactions Multiple potentially serious drug interactions may occur, and several are to be noted. Sedation and central nervous system depressant effects have a risk of respiratory depression [141] when an opioid analgesic is combined with other CNS depressant drugs, benzodiazepines and drugs that inhibit opioid metabolism, primarily CYP3A4 inhibitors, (e.g. clarithromycin or voriconazole and other anti-fungal azoles), which may markedly inhibit metabolism of oxycodone, fentanyl and methadone, as well as buprenorphine to a lesser extent). Failure of analgesia in patients who receive an opioid analgesic (μ-opioid agonist) concurrently with an antagonist at μ-opioid receptors (e.g. nalbuphine) erroneously or with a drug that induces opioid metabolism (e.g. carbamazepine, rifampicin or enzalutamide). 3/Serotonin syndrome when an opioid (especially tramadol) is combined with another drug with serotoninergic activity (e.g. SSRIs, linezolid or MAO inhibitors) or with a drug that inhibits CYP2D6 (for example, paroxetine or fluoxetine). Ventricular arrhythmia (including torsade de pointes) may arise from co-administration of methadone with another drug that prolongs the QT interval (e.g. citalopram or sertraline). Reduced anti-platelet effect of oral P2Y12 inhibitors (e.g. clopidogrel and ticlopidine) when co-administered with morphine.

3.2.4 Main Precautions for Use of Opioids in Older People

Taking into account age-related changes in drug metabolism and elimination in older people, it is necessary to modify opioid dosages when starting treatment and with ongoing management by a slower escalation of progression in dosage (no more than 30% increase each time), by adhering to the 'start low and go slow' rule [119] and with regular frequent reassessing of the efficacy and toxicity. The lowest recommended dose should be chosen for those who are the most fragile. Pain management should systematically anticipate and prevent side effects which may be more serious and unbearable for older people. The risk of drug interactions must be assessed considering polypharmacy of comorbid conditions in older people. The consequences of these interactions may lead to inappropriate discontinuation of an opioid, when excessive drowsiness in people using a combination of an opioid with other sedative drugs is incorrectly attributed to opioid intolerance. Prescribers should always check the opioid interaction risk associated with the introduction of new drugs. In the event of an acute episode that may impair renal function (dehydration, introduction of diuretics and so on), it is advisable to increase the frequency of renal monitoring to adapt the opioid dosage if necessary.

Recommendations in acute and chronic pain

- Strong opioids are important options to treat severe and very severe cancer and non-cancer pain in older people in case of the ineffectiveness of alternative options of pain pharmacotherapy.

- Prescribers should develop a good working knowledge of the different opioids and opioid formulations to perform an optimal opioid treatment.
- The choice of a specific opioid should be based on its pharmacokinetic and pharmacodynamic characteristics in adults, because the present evidence regarding older persons does not allow to recommend one opioid more than another.
- Prescribers should choose: the least invasive route of administration and favour the oral route as a first choice, taking into account the patient's ability to swallow or to apply a patch adequately. It is advisable that the titration of the effective dose is carried out with an immediate release opioid formulation administered every 4–6 h to adjust the dosage optimally based on the efficacy and side effects of the treatment. However, if not possible, an effective sustained-release formulation over 12 h can be used to titrate the effective dose from the outset.

3.3 Pharmacological Treatment of Neuropathic Pain

Neuropathic pain (NP) treatment in older people is an ongoing challenge for a number of following reasons. The intensity of pain is not a criterion for the choice of analgesic drugs, and the WHO ladder in this respect is not applicable; instead, adjuvants/co-analgesics with varied and complex pharmacologic profiles have been used at any stage of pain development, irrelevant of its severity. Dose adjustment may be limited by adverse effects with advancing age and associated comorbidities and may result in unsatisfactory analgesia. As NP is usually chronic, effective analgesic treatment must be continued for several months or years, with strict compliance, which represents another challenge in older people. Patients and the carer must be educated about adequate dosing and instructed on regular evaluation of the expected effects of treatment, including analgesia and safety.

In most patients, a systemic treatment will need to be performed, but patients with localised NP may benefit from topical agents. For systemic treatment, slow titration is necessary because of considerable inter-individual variability and poor tolerance of drugs in many older patients, particularly in relation to cognitive function. It is usual practice to start with the lowest recommended doses and to increased gradually in variable steps depending on the half-life, clearance and duration of action and according to efficacy and tolerability. Regular monitoring of their therapeutic effect after efficacy has been obtained is essential. However, depending on the drug and patient, the onset of action may be delayed from several days to several weeks and efficacy may vary, with regard to the various sensory symptoms. If the prescribed drug turns out to be ineffective, treatment should then be discontinued gradually to avoid abrupt withdrawal symptoms. Regular review of the treatment by a trained nurse at a patient's home or in a medical facility for follow-up is recommended at this stage. Ideally, education should be provided for the patient and carers, which is vital in older people with cognitive disorders. In addition to recommendations for NP treatment [96, 142], a decision-making algorithm has been proposed by a group of experts for NP management in older persons [12]. Drug treatment for NP starts with monotherapy, but if efficacy is poor, combination of adjuvant drugs with complementary mechanisms of action may be required [143]. Nevertheless, care must be taken to avoid unnecessary polypharmacy and to limit the iatrogenic risk.

3.3.1 Anti-depressants

The efficacy of tricyclic anti-depressants (TCAs) (amitriptyline, imipramine and clomipramine) is well recognised in adults for providing pain relief in NP [144]. However, their anti-cholinergic effects (visual, urinary, gastrointestinal, cardiac and neuropsychiatric) limit their applicability for pain management in older age. They may be inappropriate for older persons because of their anti-cholinergic and cardiovascular side-effects [27].

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), is recommended as a first-line treatment for painful diabetic neuropathy. Its efficacy must be assessed regularly, at least one month after initiating treatment. It should not be used in cases of severe hepatic or renal insufficiency or in patients with labile hypertension and used with caution in symptomatic tachycardia. It also entails the well-known side effects of SNRI anti-depressants, including hyponatremia resulting from inappropriate anti-diuretic hormone secretion, gastrointestinal disturbances and a variety of neuropsychiatric phenomena, particularly tremor, myalgia and visual disturbances. It is a moderate inhibitor of CYP2D6 and should be used cautiously with other drugs metabolised predominantly by this enzyme. Potent (strong and moderate) CYP1A2 inhibitors (e.g. ciprofloxacin and enoxacin) and inducers (e.g. rifampicin and phenytoin) may lead to a toxicity risk or failure of the treatment, respectively. They are also involved in many drug interactions in older persons [145].

3.3.2 Gabapentinoids

Gabapentinoid anti-epileptics are preferred to TCAs as first-line treatment of NP in older people, with a more favourable safety profile [146]. The initial dosage should be low, 25 mg/day for pregabalin and 100 mg for gabapentin, as drowsiness or dizziness leading to ataxia and falls or impaired cognitive function have been reported with higher doses. The dose should be then carefully increased, in progressive steps to reach the minimum effective dose. Side-effects should be

detected rapidly, such as peripheral oedema with pregabalin; caution should be exercised in patients with heart failure. Sedation often prevents the increase of the gabapentinoid dose or continuation of treatment. In patients with renal failure, doses of both gabapentinoids need to be adjusted. The risk of drug interactions is low, but gabapentinoids may increase the risk of somnolence and respiratory depression when used with opioids. Pregabalin is on black box in a number of European countries today [147].

3.3.3 Opioids

Tramadol appears as a second line drug in NP treatment, especially for mixed (nociceptive-neuropathic) pain when first-line drugs are ineffective. The prescription of strong opioids is generally not recommended in chronic NP. In NP of a non-cancerous origin, it is only justified, after failure of previous first-line treatment in monotherapy or in combination. Opioids may be also transiently used with caution in severe acute NP, severe neuropathic cancer pain, as rescue medication in severe episodic exacerbations of NP and/or during titration of a first-line medication to an efficacious dosage when rapid analgesia is required [148].

3.3.4 Topical Treatment

Topical treatment is to be favoured for peripheral localised NP in older patients. It targets the painful area alone, reducing the risk of adverse effects of systemic analgesics, particularly with regard to cognition and drug interactions [149, 150]. Lidocaine 5% patches are useful as first-line treatment for localised painful peripheral neuropathies, particularly pain and allodynia associated with postherpetic neuralgia (PHN). Indications may differ according to countries. It must be applied to dry, intact and non-injured skin. Local reactions (erythema, rash) may occur, and caution is recommended in patients with impaired cardiac function because of possible QT prolongation. Capsaicin 8% patches [151, 152] have shown to be equally efficacious and well tolerated in older persons as in younger patients in a recent review of randomised clinical trials. Capsaicin patches have similar analgesic efficacy in older and younger patients in terms of average pain improvement over 12 weeks. Similar proportions of older and younger patients experienced capsaicin-emergent adverse events (81.6% and 78.1%, respectively) and serious events (8.2% and 7.2%), with application-site reactions the most common in both groups.

Recommendations in neuropathic pain

- Patients must be informed that neuropathic pain treatment requires extended therapy over months or more.
- Initiation of analgesic treatment requires careful dosage adjustment.
- If monotherapy is poorly efficacious, multi-modal treatment is recommended.
- Close monitoring is mandatory and referral to a pain specialist is advised when pain is insufficiently controlled.
- Adverse drug reactions must be detected as early as possible to control the iatrogenic risks.
- Topical treatments are highly recommended for peripheral localised neuropathic pain.

3.4 Non-pharmacological Pain Treatment

International guidelines recommend the combined use of pharmacological and non-pharmacological approaches for pain management in older persons [13–19]. The focus of this present paper is on pharmacological treatment only, but experts all confirm that non-pharmacological drug treatment, psychotherapies and complementary therapies have their place in pain management of older persons and must be adapted to patients and individualised.

4 Conclusions

Optimisation of pain management in older persons relies on adequate pain detection, assessment, treatment and re-evaluation and several recommendations have been highlighted. The choice of analgesics and the route of administration require a preceding detailed pain assessment, including pain intensity, type, time pattern, quality, location (diffuse or focal), impact on sleep, functioning and quality of life, as well as an evaluation of autonomy and knowledge on current pain treatment. A full geriatric assessment with analysis of ongoing medication should be performed as limitation of the number of drugs may reduce the risk of drug interactions. Whatever the therapeutic option, kidney function must be determined and monitored during treatment, to adjust the doses of analgesics and avoid the risks of overdose. Treatment should begin with a single oral analgesic drug at the lowest dosage, increased gradually as needed according to the rule: 'start low and go slow', within the limits of maximum recommended dose, renal function and adverse effects. It is important to involve older people in their treatment, even if there is cognitive impairment, to explain the choice of medication, its expected effect, possible side effects and their management and prevention. Where appropriate, involving family members and friends facilitates therapeutic education towards better compliance and drug misuse avoidance. Systematic re-assessment of pain and treatment tolerance is mandatory. Non-pharmacological pain management interventions are strongly recommended in synergy with pharmacological approaches in older persons, especially for chronic pain.

Declarations

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