Pharmacological Treatments for Persistent Non-Malignant Pain in Older Persons

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Abstract

Persistent non-malignant pain is common, often neglected and under-treated among older persons. Some older adults do not complain because they consider chronic pain to be a characteristic of normal aging. Physicians have concerns regarding adverse effects of pharmacological treatment.

The model of the World Health Organization for treatment of cancer pain is generally accepted and also recommended for persistent non-cancer pain. Furthermore, non-pharmacological treatment should complement drug treatment when-
Pain is common among older people, but often inadequately diagnosed and treated.\textsuperscript{[1,2]} The previous neglect of this area is partly caused by the belief that older adults are less sensitive to pain and that pain is an expected consequence of aging.\textsuperscript{[3]} In many cases, the elderly also do not believe that their pain can be alleviated. Therefore, pain in older adults is less often and less aggressively treated than in younger patients.

Several epidemiological studies have shown that in community-dwelling elderly there is an age-related increase in the prevalence of persistent pain,\textsuperscript{[4,5]} joint pain\textsuperscript{[6]} and fibromyalgia.\textsuperscript{[7]} In a Swedish survey there was some evidence of decreased musculoskeletal pain with age.\textsuperscript{[5]} Among women, total reported pain decreased with age. Among men, there was an increase of reported severe pain with age. However, other studies have shown a decrease in the prevalence of pain problems for all sites, other than the joints.\textsuperscript{[8,9]} The contradictory results are probably caused by an under-reporting of pain in older adults and methodological problems (e.g. definition of chronic/acute pain). The results of studies of the prevalence of pain within samples of elderly people are more consistent.\textsuperscript{[10,11]} Roy and Thomas\textsuperscript{[12]} found that approximately 78% of younger elderly, but only 64% of older elderly, independent healthy individuals reported a current pain complaint. More recent surveys show very similar data for the prevalence of acute and persistent pain.\textsuperscript{[13,14]} In Sweden, Brattberg et al.\textsuperscript{[13]} found a prevalence of 73% for the whole study group (age >77 years) and 68% for individuals over 85 years of age.

In the institutional setting, 71–83% of patients reported at least one current pain problem which interfered with activities of daily living and quality of life.\textsuperscript{[15]} As a result of persistent pain there is not only an effect on activities of daily living, but the elderly may also be plagued by depression and anxiety, compromised cognitive function, sleep disturbance, physical disability and poor quality of life.\textsuperscript{[16-21]}

Bone and joint disorders, back problems and other chronic conditions are more common in older
adults than in younger adults. Several studies suggested that 25–50% of community-dwelling older persons have important pain problems.\textsuperscript{[22–25]} Pain is even more common in a nursing home population, but often not detected.\textsuperscript{[26–30]} However, there is evidence in both nursing home and non-nursing home populations that a significant proportion of elderly people do not receive adequate pain management.\textsuperscript{[31–33]} Pain is often treated poorly in cognitively impaired persons.\textsuperscript{[31–33]} In one study, only 16% of patients with dementia with potentially painful diagnoses received analgesic medication.\textsuperscript{[34]} The inadequate pain management is a result of many physicians lacking information about pain assessment and having an inaccurate knowledge base about pharmacological agents and non-pharmacological approaches used in pain control.\textsuperscript{[35]} One study has shown that effective pain control could be achieved in older adults compared with younger age groups by an interdisciplinary management programme.\textsuperscript{[36]}

Whether older people have a different pain perception than younger adults remains controversial. Some clinical studies suggest a relative decrease in the frequency and intensity of pain symptoms associated with myocardial complaints, visceral infections, musculoskeletal conditions, and postoperative and malignant pain problems in adults of advanced age.\textsuperscript{[37]} In other clinical studies, similarities appear more important than differences between various age groups.\textsuperscript{[37–39]} In a study by Gibson et al., there was no difference in pain perception in response to an acute heat pain stimulus in older people with cognitive impairment compared with age-matched control individuals.\textsuperscript{[40]} In general, the findings from experimentally controlled laboratory investigations are more equivocal and vary according to the type and intensity of noxious stimulation.

The negative images and stereotypes often associated with chronic pain in older people have led the American Geriatrics Society Panel on Persistent Pain in Older Persons\textsuperscript{[41]} to replace the term ‘chronic’ with ‘persistent’. The term ‘persistent pain’ may foster a more positive attitude by patients and professionals for the many effective treatments that are available to help alleviate discomfort.

The purpose of this review is to provide an overview of the different types of medications available for the management of persistent non-malignant pain and to give recommendations for specific pain conditions and diseases. Pain assessment strategies and non-pharmacological pain management modalities will also be briefly discussed. The recommendations are based on a review of existing literature indexed in MEDLINE\textsuperscript{®} and EMBASE.

1. Pain Assessment

A high prevalence of dementia, sensory impairment and disability in older persons makes pain evaluation more difficult than in a younger population.\textsuperscript{[42–46]} In addition, the elderly may be more reluctant to report painful symptoms. Often they feel that consequences of reporting pain will be need for diagnostic tests or medications. Some patients accept pain as atonement for past actions.\textsuperscript{[47]}

The evaluation process should be carried out within a comprehensive geriatric assessment because the consequences of persistent pain are numerous.\textsuperscript{[4,22]} Depression, anxiety, decreased socialisation, sleep disturbance, impaired ambulation and increased healthcare usage and costs have all been found to be associated with pain in older people. Some other conditions are worsened by the presence of pain, including gait disturbances, slow rehabilitation and adverse effects from multiple drug prescriptions.\textsuperscript{[48]} An interdisciplinary assessment is the critical first step of pain management. It is obvious that pain management is most successful when the underlying cause of pain is identified and treated. The localisation and intensity of pain reported by the patient serve as the basis for evaluation of pain.

Pain assessment instruments are also dependent on the information supplied by the patient. These instruments are either uni-dimensional measures of pain intensity or multidimensional measures of the pain experience.\textsuperscript{[49]} A variety of pain scales have been developed and some of them accepted for use among older adults. They show reliable results even in patients with mild-to-moderate dementia.\textsuperscript{[50–54]} A very popular instrument is the visual analogue scale (VAS), a 10cm line, the ends of which are anchored
with descriptors of the extremes of pain intensity such as ‘no pain’ and ‘worst pain possible’. Patients indicate which point along the line best represents their current pain. Incorrect responses to the VAS increase with age. Herr and Mobily found that a vertical orientation might be more appropriate for the elderly. The Faces Pain Scale has been shown to have good test-retest reliability and construct validity in older adults. Herr and Mobily found the pain thermometer, a modified vertical verbal descriptors scale, to be the easiest to use and the best to describe pain. The verbal descriptor scale may be used effectively in the assessment of pain in the elderly with a wide range of cognitive function.

In a comparative study of four different scales for the assessment of pain, it was demonstrated that a horizontal 21-point box scale was the best scale for pain assessment in older patients, including those with mild cognitive impairment. In a study of pain assessment in cognitively impaired nursing home residents, most patients with mild-to-moderate cognitive impairment could be assessed using at least one of the four uni-dimensional bedside assessment scales. Observational scales must be used among those with moderate cognitive impairment. Behavioural manifestations of pain, such as grimacing, noisy breathing, sighing, moaning, staying in bed and agitation have been shown to correlate well with pain self-report measures. Unusual behaviour in those patients should trigger pain assessment to identify any potential cause.

Multidimensional pain instruments that evaluate pain in relation to other domains are more complex and time consuming. Because these tools were designed for use with younger adults the data regarding their appropriateness for elderly patients remain controversial.

2. Pain Management

2.1 Non-Pharmacological Treatment

Pharmacotherapy is the most common treatment to control pain in older persons, though there are many risks associated with polypharmacy. Older persons are generally more susceptible to adverse drug reactions. Thus, non-pharmacological management techniques should be implemented whenever possible. The physical and psychological treatments often require active participation. Physical therapies such as heat, massage, stretching and muscle release techniques have shown to be effective depending upon the underlying modalities for persistent pain. Transcutaneous electrical nerve stimulation has been shown to help individuals with post-herpetic neuralgia and low back pain. Physiotherapy is helpful in persistent pain syndromes caused by osteoarthritis and osteoporotic fractures. It was demonstrated that even walking can lead to pain relief in patients with osteoarthritis or lower back pain.

Behavioural therapy and learning of coping strategies may help to control pain. The most effective forms of cognitive behavioural therapy use a structured systematic approach to teaching coping skills. Education programmes alone can lead to pain relief and better management. Although there is limited research evidence, application of heat or ice on the painful sites can give prompt relief to the patient and offers occasion for personal devotion.

There is a growing body of literature on complementary or alternative therapies with different results, but it is beyond the scope of this review to describe these therapeutic strategies in more detail.

2.2 Pharmacological Treatment

Pharmacological treatment is the basis of pain management, but older patients often have impaired hepatic and renal functions. There is also an increased sensitivity to CNS active drugs, including opioid analgesics. Changes in pharmacodynamics and pharmacokinetics in older adults lead to differences in efficacy, sensitivity and toxicity compared with younger adults. Therefore, one major rule in the pharmacological treatment of pain is to start with the lowest anticipated effective dose and then titrate the dose on the basis of likely steady state blood levels and clinically demonstrated effects.

The model of the World Health Organization (WHO) for treatment of cancer pain is generally...
accepted and also recommended for persistent non-cancer pain. Although no longer considered relevant as a step care approach in most cases it makes sense to start with non-opioid analgesics, especially in patients with musculoskeletal pain.

For the relief of severe pain, opioid analgesics are recommended. Their use is also becoming more acceptable in persistent non-cancer pain, since longitudinal studies have shown that tolerance is slowly developed in the face of stable disease and the risk of drug dependency and addiction is low when these drugs are administered orally. The risk of addiction to opioids is <1%. There are no reasons to withhold opioids from older patients. Some specific recommendations and rules should be considered when starting with pharmacological treatment of persistent pain in the elderly (table I). For compliance, drug regimens should be simplified as much as possible and regimens should be adjusted to meet individual needs and lifestyles. For continuous pain, medication should be given on a fixed schedule. Whenever possible, sustained-release formulations should be used with supplemental doses of immediate release, short-acting analgesics, if necessary.

### 3. Mild Pain

For the most frequent conditions that induce pain in the elderly, such as osteoarthritis, low back pain or peripheral neuropathy, the analgesics recommended for step one of the WHO step care approach are at the first choice. NSAIDs, paracetamol (acetaminophen) or dipyridamole (pyrazolone) are effective for either mild-to-moderate pain in the elderly or as a co-analgesic with opioids for more severe pain.

#### 3.1 Classic NSAIDs

NSAIDs play a major role in the management of acute and chronic pain syndromes in all age groups and are among the most widely prescribed class of drugs in the world. Most frequent indications for their use in the elderly are osteoarthritis or inflammatory conditions, such as rheumatoid arthritis. However, NSAIDs do not seem to have beneficial effects on the pathophysiology of joint destruction in osteoarthritis, but they do reduce pain and improve function. It is not known whether this is more attributable to their anti-inflammatory or analgesic effect. Recommendations for the use of some NSAIDs are shown in table II.

<table>
<thead>
<tr>
<th>Table I. Principles of medical management of persistent pain in the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Administer a combination of pharmacological and non-pharmacological treatment</td>
</tr>
<tr>
<td>2. Drugs should preferably be given:</td>
</tr>
<tr>
<td>• by mouth</td>
</tr>
<tr>
<td>• by the time (fixed time schedule, instead of application upon request)</td>
</tr>
<tr>
<td>• using the World Health Organization step care approach, however, patients with severe, disabling pain should not necessarily proceed through the initial steps</td>
</tr>
<tr>
<td>3. Long-acting or sustained-release analgesic preparations should be used for continuous pain</td>
</tr>
<tr>
<td>4. Breakthrough pain should be treated by fast-onset, short-acting preparations</td>
</tr>
<tr>
<td>5. Start low, go slow (the least toxic means of achieving systemic pain relief should be used)</td>
</tr>
<tr>
<td>6. NSAIDs should be avoided for long-term use (particularly in patients with a history of gastrointestinal bleeding and/or ulcers)</td>
</tr>
<tr>
<td>7. Cyclo-oxygenase-2 selective inhibitors should be used with caution in patients with renal failure, heart failure and hypertension</td>
</tr>
<tr>
<td>8. A combination of non-opioids, opioids and adjuvant drugs should be considered whenever possible to reduce the risk of adverse effects from high doses of a single agent and to enhance pain relief</td>
</tr>
<tr>
<td>9. Fixed-dose combinations of opioids with paracetamol (acetaminophen) or NSAIDs may be useful for mild-to-moderate pain</td>
</tr>
<tr>
<td>10. When using opioids adverse effects that may be particularly problematic for the elderly should be anticipated and managed: constipation, sedation, cognitive impairment, orthostatic hypotension, nausea, and urinary retention</td>
</tr>
<tr>
<td>11. A regular re-evaluation of the drug therapy is pertinent</td>
</tr>
<tr>
<td>12. Clinical endpoints should, at a minimum, include decreased pain, improvements in mood and sleep and better functional abilities</td>
</tr>
</tbody>
</table>

Most NSAIDs act by inhibiting cyclo-oxygenase (COX) which catalyses the conversion of arachidonic acid to prostaglandins (PGs), thereby blocking the synthesis of proinflammatory PGs. In the 1990s there was the discovery of two isoenzymes of the COX, COX-1 and COX-2, which catalyse the conversion of arachidonic acid to PGH₂. While COX-1 is expressed constitutively in most tissues and is necessary for the synthesis of gastroprotective PGs,
Table II. Some properties of commonly used NSAIDs for persistent non-malignant pain in the elderly\cite{94, 106-110}

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Plasma binding (%)</th>
<th>Elimination half-life (h)</th>
<th>Individual dose (mg)</th>
<th>Maximum daily dose (mg)</th>
<th>Dose frequency</th>
<th>Administration for geriatric patients (oral administration)</th>
<th>Recommendation for geriatric patients (oral administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>60–80</td>
<td>3–4</td>
<td>100–3000</td>
<td>4000</td>
<td>tid to qid</td>
<td>Oral, parenteral</td>
<td>**</td>
</tr>
<tr>
<td>(acetylsalicylic acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>100</td>
<td>1–2</td>
<td>25–75</td>
<td>150</td>
<td>bid</td>
<td>Oral, parenteral, topica</td>
<td>***</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>99</td>
<td>2</td>
<td>200–800</td>
<td>2400</td>
<td>tid</td>
<td>Oral, topical</td>
<td>***</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>99</td>
<td>2–11</td>
<td>25–75</td>
<td>200</td>
<td>tid</td>
<td>Oral, topical</td>
<td>**</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>99</td>
<td>2–4</td>
<td>25–100</td>
<td>200</td>
<td>tid to qid</td>
<td>Oral, topical</td>
<td>*</td>
</tr>
<tr>
<td>Naproxen</td>
<td>99</td>
<td>12–15</td>
<td>250–500</td>
<td>1000</td>
<td>bid</td>
<td>Oral, topical</td>
<td>**</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>99</td>
<td>14–160</td>
<td>20–40</td>
<td>40</td>
<td>od</td>
<td>Oral, topical</td>
<td>*</td>
</tr>
</tbody>
</table>

\textit{bid} = twice a day; \textit{h} = hours; \textit{od} = once daily; \textit{qid} = 4 times daily; \textit{tid} = 3 times daily; * indicates not recommended; ** indicates less recommended; *** indicates recommended.

the COX-2 gene activity and protein production is highly regulated.\cite{98}

The COX-2 isoenzyme is nearly undetectable under normal physiological conditions, except in the CNS, renal cortex and vasa deferentes, but it can be induced by endotoxin, interleukin-1, tumour necrosis factor-\alpha and some more exo- and endogenous agents.\cite{96} It increases markedly in joint inflammation.\cite{99}

The classic NSAIDs inhibit both isoforms of COX. The inhibition of COX-1 is mainly responsible for the gastrointestinal and renal toxicity of the classic NSAIDs. With the introduction of specific COX-2 inhibitors there was initially great euphoria about the good analgesic effect and the supposed lack of relevant adverse effects, but today there is more evidence of potentially harmful adverse effects, especially in the elderly.\cite{99}

The prototypic NSAID is aspirin (acetylsalicylic acid), which was discovered to be an analgesic and antipyretic drug in 1899. Today there are more than 30 chemically different NSAIDs available on the market.\cite{100} NSAIDs are among the most commonly prescribed drugs for the elderly in the world.\cite{101} For their widespread use (not only prescription, but also over-the-counter) their actions, benefits and risks have to be well-known among all doctors treating elderly people.\cite{102} In general, the analgesic potency of NSAIDs at equal standard dosages is similar and dose escalation beyond a certain level does not produce additional analgesia.\cite{103, 104} Differences exist in the latency of onset and duration of effect, excretion half-life and, therefore, interval of dosage, mode of administration and location and severity of adverse effects (table II). Most NSAIDs are weak acids and therefore accumulate in inflamed tissues, which is of advantage in terms of getting high drug concentrations at the site of pain, but there is also a high affinity for blood, bone marrow, liver, kidney and the wall of gastrointestinal tract.\cite{105}

All NSAIDs can cause nausea, dyspepsia and epigastric discomfort in various amounts. More severe gastrointestinal complications include gastric or duodenal ulceration, diarrhoea, perforation or ulceration of the colon.\cite{106, 108} NSAID users are at approximately 3-fold greater relative risk than non-users for developing serious adverse gastrointestinal events.\cite{106} Nearly a quarter of elderly persons living in long-term care facilities regularly use NSAIDs. This frail population already has a 5- to 6-fold greater risk of serious gastrointestinal events than non-institutionalised elderly. Moreover, NSAID users are particularly vulnerable to gastrointestinal adverse effects with a 2- to 3-fold greater risk than non-users, and clinical symptoms of gastric or duodenal ulceration are often modest in the elderly.\cite{111} Despite the dose dependency of gastrointestinal adverse effects of all NSAIDs, there is evidence for lower risk with ibuprofen and diclofenac, intermediate risk with indomethacin and naproxen and highest risk with ketoprofen and piroxi-
However, compared with paracetamol or dipyridamol, the overall excess mortality for common NSAIDs is considerably higher (figure 1).\[^{113}\]

Adjunction of misoprostol, a PG analogue, can antagonise the gastric damage of NSAIDs.\[^{114}\] Fixed-combination drugs are available in the market. Their use is limited by the high price and frequent incidence of diarrhoea.\[^{115}\] The adjunction of proton-pump inhibitors (such as omeprazole) can prevent NSAID-induced gastric damage or recurrent ulcer bleeding.\[^{116,117}\] The use of these adjuncts is limited by the high cost and potential interaction with other drugs, but should be undertaken if long-term use of an NSAID in geriatric patients is necessary.\[^{118}\]

Moreover, there is evidence that NSAIDs exert negative effects on the cardiovascular system. This is thought to be caused by the elevation of blood pressure.\[^{119}\] The increase is remarkable, with a 5.4 mm Hg increase of mean arterial blood pressure found in a meta-analysis.\[^{120}\] Considering the results of the Hypertension Optimal Treatment study\[^{121}\] or the UK Prospective Diabetes Study,\[^{122}\] it is obvious that consequences such as stroke, congestive heart failure or renal insufficiency must be carefully evaluated against the benefits of the drug.

Fluid retention is common in patients using NSAIDs because of an increase in sodium reabsorption in the ascending limb of the loop of Henle.\[^{96}\] The effects are generally mild, but 3–5% of older patients receiving NSAIDs develop serious renal adverse effects such as weight gain, oedema, hypertension and congestive heart failure.\[^{96}\] NSAIDs may occasionally produce acute renal failure in the elderly.\[^{123}\] The pathogenesis is believed to be renal vasoconstriction secondary to inhibition of vasodilatory PGs with unopposed vasoconstrictor forces, including angiotensin II, catecholamines and enhanced sympathetic activity.\[^{124}\] Finally, most NSAIDs can contribute to the development of chronic renal failure, especially when renal damage is already present.\[^{125,126}\] In particular, older adults receiving concomitant therapy with diuretics or ACE inhibitors are at high risk of developing renal failure.\[^{127}\] Nonacetylated salicylates, such as choline magnesium trisalicylate or salarse, are less nephrotoxic and do not inhibit platelet aggregation.\[^{128}\] Other adverse effects of NSAIDs seen in the elderly are agitation, confusion and tinnitus.\[^{115}\]

Because of serum-protein binding there is interaction between NSAIDs and other drugs often used by geriatric patients, such as warfarin, digoxin, oral antidiabetics or antihypertensives, especially ACE inhibitors and diuretics.\[^{45,115}\] For all these reasons, systemic NSAID therapy should not be continued indefinitely, but be reviewed after an inflammatory process is suppressed or the pain-generating condition has ceased.

As topical therapy, most NSAIDs are effective in reducing pain.\[^{129–131}\] The topical route is very well accepted by geriatric patients and when application is done by assisting persons, such as nurses or family members, it also gives a great psychological relief. For osteoarthritis with chronic pain, topical diclofenac seems to be effective with little adverse effect,\[^{112}\] while topical ketoprofen has shown effectiveness in acute injuries.\[^{133}\] Meloxicam, nimesulide, etodolac and nabumetone are also selective COX-2 inhibitors.\[^{134}\] New drugs, such as acemetacin\[^{135}\] or tepoxalin,\[^{136}\] that also inhibit 5-lipoxygenase, may offer some advantages. To date, there are not enough data to recommend their use in geriatric patients.

![Fig. 1. Overall excess mortality with NSAIDs and other non-narcotic analgesics (reproduced from Andrade et al.\[^{115}\] with permission from Elsevier).](image-url)
3.2 Cyclo-oxygenase-2 Inhibitors

The discovery of the two isoforms of COX in the 1990s was followed by the development of specific COX-2 inhibitors, of which celecoxib and rofecoxib are used worldwide today. At therapeutic concentrations celecoxib and rofecoxib inhibit COX-2, but do not inhibit COX-1.\[^{113}\] They differ in their chemical structure, metabolism and other pharmacological properties, but have some properties in common. At steady state, elderly subjects had a 34% and 50% higher area under the plasma concentration-time curve compared with the young subjects for rofecoxib and celecoxib, respectively. Both drugs can interact with warfarin, but they do not interact with methotrexate at doses used for treating rheumatoid arthritis.\[^{96}\]

Celecoxib was introduced in 1998 to the US market and since 2000 it has also been used in Germany and other European countries for the treatment of osteoarthritis and rheumatoid arthritis.\[^{138}\] Chemically it is a sulphonamide based on 1,5-diarylpypyrazol and there is possible cross-sensitivity in case of sulphonamide sensitivity. With a half-life of 11 hours, it is administered once or twice daily in osteoarthritis and twice daily in rheumatoid arthritis (100–200mg once or twice daily).\[^{131}\] Celecoxib undergoes extensive hepatic metabolism via the cytochrome P450 (CYP) system, specifically CYP2C9, CYP2C19 and 2D6, so interactions with flunonazole, antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors) or β-adrenoceptor antagonists are possible.\[^{96,138}\]

The Celecoxib Long-term Arthritis Safety Study (CLASS)\[^{139}\] examined the gastrointestinal safety of high doses of celecoxib (400mg twice a day) in more than 4000 patients; use of low-dose aspirin was allowed for cardiovascular risk patients (21%). Patients in the celecoxib group had a lower incidence of symptomatic ulcers compared with the NSAID group for the non-aspirin taking patients and no significant increase in cardiovascular events compared with diclofenac or ibuprofen users. In addition, celecoxib patients had less hypertension and oedema.\[^{139,140}\] It is important to note that the gastrointestinal advantages were found only in the non-aspirin users, and only 6-month data were published; most gastrointestinal complications happened beyond this time.\[^{141}\] A recently published systematic review of randomised controlled trials found equal effectiveness of celecoxib compared with classic NSAIDs, but improved gastrointestinal safety and tolerability.\[^{142}\] The risk of recurrent ulcer bleeding among high-risk patients was equal in patients taking celecoxib 200mg twice daily compared with patients taking extended-release diclofenac 75mg twice daily plus omeprazole 20mg daily.\[^{117}\]

Rofecoxib is a methyl sulfone with a half-life of 10 hours and is administered once daily.\[^{143}\] Rofecoxib is approved for the treatment of osteoarthritis and rheumatoid arthritis at a dosage of 12.5 or 25mg once daily, and for acute pain and dysmenorrhea at a dosage of 50mg once daily. Analgesic and anti-inflammatory properties are comparable with other NSAIDs in standard dosages.\[^{144}\] In patients with osteoarthritis of the knee or hip, rofecoxib at a dosage of 25mg was slightly less effective than diclofenac in patient’s assessment of response to therapy and physician’s assessment of disease status.\[^{145}\]

Gastrointestinal toxicity with rofecoxib is low. In the VIOxx\(^\oplus\) Gastrointestinal Outcomes Research (VIGOR) study it was calculated that only 41 patients would need to be treated with rofecoxib 50mg once daily rather than naproxen 500mg 3 times daily to avert one clinical upper gastrointestinal event in a 1-year period;\[^{101}\] efficacy on pain after 9 months of treatment was similar for the two drugs. Risk reduction of clinical gastrointestinal events among patients in the rofecoxib group as compared with those in the naproxen group was 50%. Also, rofecoxib at 10-fold supra-therapeutic dosages had been found to have few gastrointestinal adverse effects,\[^{143}\] but recently it was shown that there was a higher risk of upper gastrointestinal haemorrhage with rofecoxib than with celecoxib at standard dosages.\[^{146}\] The incidence of cardiovascular events in the rofecoxib group was remarkably higher compared with napro-

\[^{1}\] The use of tradenames is for product identification purposes only and does not imply endorsement.

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xen group in the VIGOR study. A 4-fold increase of myocardial infarction in the rofecoxib group compared with the celecoxib group (0.4% versus 0.1%) in VIGOR cannot be fully explained. Aspirin was precluded at entry to VIGOR, while in the CLASS study, one-fifth of patients were taking aspirin which is a cardioprotective agent. Recently, a retrospective cohort study showed that users of rofecoxib 50mg were 1.7 times more likely to have serious coronary heart disease than NSAID non-users, but there was no such evidence at dosages of 25mg or less.

Another important aspect comes from the Successive Celecoxib Satisfaction and Effectiveness in Osteoarthritis (SUCCESS IV) study, which compared celecoxib 200mg once daily to rofecoxib 25mg once daily over 6 weeks in osteoarthritis patients aged ≥65 years who were also taking anti-hypertensive agents, a frequent concomitant treatment among the elderly. It was found that nearly twice as many rofecoxib- compared with celecoxib-treated patients experienced oedema (9.5% versus 4.9%); systolic and diastolic blood pressure increased significantly in patients receiving rofecoxib; and in the rofecoxib group four patients developed congestive heart failure. For celecoxib it was shown that in ACE-inhibitor-treated patients there was no influence on blood pressure in a 4-week trial.

Both celecoxib and rofecoxib can influence renal function as the classic NSAIDs do. So attention should be paid to the decreased sodium excretion, development of hyporeninemic hypoaldosteronism with hyperpotassaemia and reduction of glomerular filtration rate, especially under low-sodium diet.

Recently parecoxib, a new COX-2 inhibitor for parenteral use, was introduced to the German market for treatment of postoperative pain. It is a prodrug of valdecoxib and has a rapid onset of analgesic effect (around 15 minutes after intravenous administration) and analgesic action comparable to ketorolac. Adverse effects include anaphylaxis, particularly in patients with sulphonamide allergy. Recently, anaphylactoid reactions, such as urticaria, angioedema and hypotension, were reported with all COX-2 inhibitors.

It is not possible to discuss all aspects of the COX-2 inhibitor study data. Generally, it is agreed that COX-2 inhibitors offer advantages over classic NSAIDs for their use in the elderly because of their better gastrointestinal tolerability. The once-daily administration and small tablet size of rofecoxib are advantageous for compliance in the elderly. However, the safety profile with respect to cardiovascular and renal effects favours celecoxib at the moment. The high cost of COX-2 inhibitors along with incompletely understood cardiovascular and renal adverse effects, lack of data on long-term safety and an incompletely understood role in certain physiological conditions (e.g. gastric ulcer healing), means that these drugs should be carefully evaluated before their widespread use.

3.3 Other Drugs

3.3.1 Paracetamol (Acetaminophen)

Paracetamol (4-hydroxyacetonilid) is an analgesic and antipyretic drug known since 1878. It is used worldwide across all age groups as it has modest adverse effects at therapeutic dosages. The efficacy of paracetamol appears to be equivalent to that of ibuprofen (e.g. in the treatment of osteoarthritis of the knee). Generally its use is limited to mild pain or as an adjuvant with opioids for more severe pain. The mechanism of action is not known; there is a presumptive central effect, but no peripheral anti-inflammatory or anti-platelet activity. The drug is well absorbed after oral ingestion mainly in the duodenum. Rectal administration is also possible, which is useful in case of nausea or if tablets are not well tolerated. Paracetamol is administered in doses of 500–1000mg at a time and should be limited to a maximum of 4 g/day in four divided dosages.

Paracetamol is the main metabolite of phenacetin, which was withdrawn from the market because of its induction of interstitial nephritis. In general, paracetamol has a good safety profile when used for the treatment of pain in geriatric patients. However, excessive short-term (>15 g/day) or long-
term (>5 g/day) use can cause hepatotoxicity.\textsuperscript{160-162} It is not clear whether fasting conditions or excessive consumption of ethanol can increase the risk of paracetamol-induced hepatotoxicity with standard dosages (<5 g/day).\textsuperscript{163,164} In the event of an overdosage there is serious risk of severe liver damage or death, thus, good patient information is mandatory.\textsuperscript{165}

The small incidence of drug interactions, e.g. with warfarin,\textsuperscript{166} and complete lack of gastrointestinal damage potential with paracetamol have advantages in treating geriatric patients. In only one retrospective study there was an enhanced risk of chronic renal failure with long-term use of paracetamol.\textsuperscript{126}

Paracetamol is used in combination with opioids if pain is more severe. Fixed-dose combinations of paracetamol and codeine are available in most countries with contents of 500–1000mg paracetamol and 8–60mg codeine. In the elderly, single administration of the fixed-dose combination gives better pain relief than paracetamol alone, with few adverse effects like sedation. With repeated-dose or long-term use more adverse effects such as nausea and dizziness are reported.\textsuperscript{167,168} Owing to its lack of anti-inflammatory action, the use of paracetamol in inflammatory diseases (e.g. rheumatoid arthritis) is limited and classic NSAIDs should be prescribed for such conditions.\textsuperscript{169}

3.3.2 Dipyrone (Pyrazolone)

Dipyrone was introduced for the treatment of fever and pain in 1922. Because of an apparently unacceptable risk of agranulocytosis it was withdrawn from the US market in 1977, but it is still in use in Germany and other European countries.\textsuperscript{170} Agranulocytosis arising from the use of dipyrone is not dose-dependent and is potentially life threatening. The reported incidence of agranulocytosis with dipyrone in Sweden after its re-introduction in 1995 was estimated to be at least 1 in 1439 prescriptions.\textsuperscript{171} The risk of developing a serious idiosyncrasy varies in different geographic areas.\textsuperscript{172}

The analgesic efficacy of dipyrone is superior to paracetamol and comparable to aspirin.\textsuperscript{173} The mechanism of action is not well understood; there is a presumptive central and peripheral effect. Usual dosage is between 8 and 16 mg/kg bodyweight, with a maximum dosage of 4 g/day. The drug can be given orally (drops or tablet), rectally, intravenously or intramuscularly. After an oral dose the drug is hydrolysed to 4-N-methylaminoantipyrin, which is the active metabolite. This has an antipyretic, analgesic and spasmyloytic effect on smooth muscles (on the Oddi sphincter and the urinary system).\textsuperscript{119} In the elderly the elimination half-life of the metabolite is doubled, with a good correlation between total body clearance and creatinine clearance.\textsuperscript{174} The manufacturers recommend a careful reduction of maximal dosage in the elderly because of the presumptive hepatic or renal insufficiency.\textsuperscript{175}

Adverse effects relevant to the elderly include hypotension, especially with fast intravenous administration, which, therefore, should be avoided. Severe adverse effects include anaphylaxis, agranulocytosis, aplastic anaemia, Stevens-Johnson syndrome and toxic epidermal necrolysis, upper gastrointestinal complications and renal failure.\textsuperscript{176} The global excess mortality risk appears to be substantially lower than that associated with equipotent doses of NSAIDs,\textsuperscript{113,170} as shown in figure 1.

In Europe, the use of dipyrone in the treatment of acute pain in the elderly is widespread because of the well-accepted oral administration with drops and its ability to relieve pain of any origin. It can be combined with opioids or other agents, with no CNS adverse effects.\textsuperscript{176} The lack of anti-inflammatory action limits its use in frequent conditions such as osteoarthritis or rheumatoid arthritis. For homecare, the need for frequent administration (its duration of effect is only 4 hours) is a disadvantage. Regular blood counts and monitoring of blood pressure, especially with intravenous administration, should be done.

4. Moderate Pain

According the WHO model for moderate pain, a combination of non-opioid analgesics and opioid analogues with moderate pain relief properties is recommended (e.g. oxycodone, codeine, tramadol and tilidine/naloxone). Often these opioids are used
in a fixed-dose combination with non-opioid analgesics using additive pharmacology. The use of fixed-dose combination products is limited by the ceiling effect and the potential toxicity associated with the non-opioid agent.

Tramadol is an analgesic with a dual mechanism of action: opioid mu receptor binding combined with a blockage of norepinephrine uptake. Tramadol has a low abuse and diversion potential.\[177-179\] There is limited information regarding the tolerability of this agent in frail elderly people, but its adverse effect profile is similar to that of equianalgesic doses of codeine and hydrocodone, including the potential for drowsiness and nausea. Tramadol has shown its effectiveness in reducing mild-to-moderate pain associated with osteoarthritis, low back pain and diabetic neuropathy.\[180-183\]

According to the manufacturer, reduced doses should be administered in those aged 75 years and over and in patients with renal failure (creatinine clearance <30 mL/min).\[184\] Tramadol should be used with caution in patients with a history of seizure disorders because in rare cases, seizures can occur as an adverse drug reaction of tramadol. A possible serotonin syndrome must be considered when using tramadol concomitantly with other serotonergic drugs.\[176\]

Hydrocodone is used in fixed-dose combinations with paracetamol or NSAIDs. It is recommended for acute recurrent, episodic or breakthrough pain.\[41\]

Controlled-release oxycodone has shown its effectiveness for reducing pain in osteoarthritis.\[185\] It is also effective in the treatment of cancer-related moderate pain.\[186,187\] Oxycodone and codeine are effective in a prolonged treatment of rheumatic disease in reducing pain severity.\[188\]

Single entity controlled release codeine is an effective treatment for pain caused by osteoarthritis of the hip or knee.\[189\] In a systematic review of 29 controlled trials, a paracetamol/codeine combination showed a slightly higher, but statistically significant analgesic effect than paracetamol alone.\[167\]

A fixed-dose combination of tilidine/naloxone is available in Belgium and Germany. It contains the prodrug tilidine from which the active metabolite nortildine is formed by demethylation in the liver,\[190,191\] and the opiate antagonist naloxone which prevents the abuse of the analgesic by opiate dependents. In contrast to other opioids, such as pentazocine, tilidine does not affect sphincter of Oddi motility.\[192\] Therefore, tilidine can be used for analgesia in pancreaticobiliary disease. The competitive opiate antagonist naloxone is not able to prevent ventilatory depression in massive overdoses.\[193\] In one study tilidine/naloxone showed a favourable benefit-risk ratio for use in long-term treatment of chronic pain.\[194\] A reduction of the dose of tilidine in patients with severely impaired kidney function does not seem to be required.\[195\]

5. Severe Pain

In the WHO model for severe pain a combination of non-opioid analgesics and opioid analgesics with strong pain relief properties is recommended.

Older adults show an increased pharmacodynamic sensitivity to opioid analgesics.\[196-198\] There are age-related changes in opioid pharmacokinetics that have been examined for morphine, pethidine and fentanyl. These opioids have a longer half-life, reduced clearance and higher maximal plasma concentrations in older adults compared with younger individuals.

The opioids should be administered orally. With the exception of pethidine and fentanyl they are well absorbed via the oral route. Sublingual absorption is relatively high for buprenorphine, methadone and fentanyl.\[199\]

For most opioids, the liver is the major site of biotransformation and the major metabolic pathway is oxidation. The exceptions are morphine and buprenorphine, which primarily undergo glucuronidation.\[200\] Thus, in chronic liver disease, lower doses or longer administration intervals should be used to prevent the risk of accumulation of drug in the body.

5.1 Morphine

Morphine primarily undergoes liver metabolism via phase II biotransformation and yields two active metabolites, morphine-6-glucuronide and mor-
phine-3-glucuronide. These active metabolites are renally cleared and can, therefore, accumulate in patients with renal dysfunction. Several studies have shown that parenteral morphine has a longer half-life, reduced clearance and higher maximal plasma concentrations in older adults compared with younger individuals.

5.2 Pethidine

Pethidine has only limited oral potency because of a significant first-pass effect. The active metabolite normeperidine may accumulate when pethidine is given regularly. This can cause CNS hyperirritability with nervousness, tremors, myoclonus and/or seizures. In liver disease with reduced drug metabolism, there is an accumulation of normeperidine, increasing the risk of seizures.

5.3 Codeine and Tilidine

The analgesic activity of codeine and tilidine depends on transformation into the active metabolites, morphine and nortilidine, respectively. If metabolism is decreased in patients with chronic liver disease, the analgesic action of these drugs may be compromised. The disposition of a few opioids such as fentanyl, sufentanil and remifentanil appears to be unaffected in liver disease.

5.4 Fentanyl and Buprenorphine

Fentanyl and buprenorphine are now available as transdermal preparations in the market. Fentanyl is very popular when given as a patch. In comparison to sustained-release oral morphine, transdermal fentanyl is preferred by patients with cancer pain and chronic non-cancer pain, mainly because of better pain relief achieved with less constipation and an enhanced quality of life. It is also effective in the prolonged treatment of neuropathic pain. But so far there are only limited data available in older adults. The same is also true for buprenorphine skin patches. Buprenorphine is a partial morphine antagonist and has a ceiling effect. There are wide interindividual differences in absorption and equipotential analgesic doses to oral morphine in older adults. Even the smallest patches of fentanyl or buprenorphine may be too potent for frail older adults. The transdermal application should be considered for those patients who can not take oral medication or drugs which are rectally administered. To what extent the transdermal drug is better tolerated in older patients than the sublingual application remains to be clarified. In our own experience, some patients respond better to these drugs than to other opioids and have fewer adverse effects.

5.5 Hydromorphone

Hydromorphone is recommended for breakthrough pain or for around-the-clock administration and when morphine fails to produce sufficient pain relief (despite increase of doses) or causes intolerable adverse effects (despite treatment of symptoms). In a systematic review, Quigley and Wiffen found little difference between hydromorphone and other opioids in terms of analgesic efficacy, adverse effect profile and patient preference.

5.6 Dextropropoxyphene and Pentazocine

Several opiates including dextropropoxyphene and pentazocine are not recommended for use in older adults, because of their potential for toxicity and lack of efficacy.

When taking opioids, careful monitoring is required for potential adverse effects focussing on neurologic, gastrointestinal and cognitive-behavioural effects, such as sedation, nausea, vomiting, constipation, urinary retention, respiratory depression, falls/fractures and cognitive impairment. Serious adverse effects often can be avoided when at the start low doses are given and escalated gradually. Opioids are not end-organ toxic. Sustained-release opioid formulations are available for most of the common drugs used for continuous treatment of moderate-to-severe pain. Patients should be informed not to chew or crush continuous release tablets, because this may lead to a rapid absorption of the entire dose resulting in overdosage. Long-acting opioids should require additional monitoring, because of the possibility of a relatively long period till steady state is approached.
Because of practical considerations (e.g. patients with cognitive impairment will probably swallow the drugs) and based on our own experience, sublingual application (e.g. buprenorphine) can not be recommended in elderly patients with cognitive impairment.

6. Adjunctive Agents

So-called adjuvant drugs, developed for other purposes, can be added to analgesics therapy. These drugs have the potential to alter, attenuate or modulate pain perception. The pain-modulating drugs are additionally used to treat many persistent pain conditions, especially neuropathic pain. Some adjunctives, used for managing postoperative pain or nausea, such as antihistamines, phenothiazines or benzodiazepines, should be avoided in the elderly because of the increased risk of delirium.[228] Appropriate adjunctive agents for use in the elderly are briefly summarised.

6.1 Antidepressants

The mechanism of action of tricyclic antidepressants in the management of pain is not completely understood. These agents block α1-adrenergic, muscarinic and histamine H1 receptors, and also serotonin and norepinephrine reuptake.[229] It is thought that the latter is primarily responsible for the analgesic effect involving supraspinal and spinal modulator pathways.[230] The effect is particularly good on neuropathic pain, such as in diabetic or postherpetic neuropathy, and is already given at low dosages, apparently not conjugated to a significant antidepressive effect. The best evidence exists for the effects of amitriptyline, but desipramine, imipramine, clomipramine, doxepin and maprotiline have also been studied.[231,234] No effect was found for other antianxiety agents, such as hydroxyzine, prochlorperazine or chlorzepoxide.[235] For the newer selective serotonin reuptake inhibitors (SSRIs), controversial data exist.[236,237] Citalopram, paroxetine and venlafaxine were shown to be effective in the treatment of diabetic neuropathy in placebo-controlled trials.[238-240] It is always useful to treat concomitant depression adequately because of the suggested higher pain sensitivity in depressive patients.[194,230]

The use of SSRIs in the elderly is beneficial as these agents have few adverse effects. The frequent anticholinergic adverse effects of tricyclic antidepressants have to be carefully monitored. These include glaucoma, urinary retention, prolongation of the atrioventricular interval and induction of cardiac arrhythmia, confusion and sedation with possibility of falls.[231] Some tricyclic antidepressants such as nortriptyline, desipramine or lofepramine have less anticholinergic adverse effects.[241]

6.2 Antiepileptic Drugs

Anticonvulsants are useful in the suppression of neuropathic pain, such as painful diabetic neuropathy, post-herpetic or trigeminal neuralgia or post-stroke pain.[230,242] Carbamazepine, valproic acid and phenytoin are generally used. Central adverse effects, such as sedation, drowsiness or confusion, have to be carefully monitored and may require a very slow dose titration. For example, the starting dose of carbamazepine syrup would be 50mg at bedtime, with 50mg increments weekly up to a maximum dosage of 400 mg/day of a controlled release, divided in two doses.

In recent years there has been increasing use of gabapentin because of its lack of hepatotoxicity, which often limits the use of anticonvulsants in long-term therapy and the few adverse effects observed in the elderly.[243] The adverse effects are mainly sedation and dizziness, which can cause falls, especially in the presence of afferent ataxia in patients with severe diabetic neuropathy.[244,245] Gabapentin has been found to be effective in painful diabetic neuropathy,[244] post-herpetic[243] or trigeminal neuralgia,[246] restless legs syndrome,[247] phantom limb and stump pain[248] and post-stroke pain.[249] The starting dose is 100–300mg at bedtime, then gradually increasing to 1800–3600mg divided in three doses.[250] The maximum dose of 3600mg should be avoided in the elderly because of the renal clearance of the drug.[45,230]

Newer anticonvulsants such as lamotrigine, topiramate or tiagabine have shown analgesic ac-
tion.\textsuperscript{[251,252]} Although they are not currently licensed for treating pain, they could be considered if there is no response with gabapentin.

6.3 Other Adjunctive Agents

Capsaicin, a vanilloid receptor agonist, is a topical agent derived from cayenne pepper.\textsuperscript{[253]} It depletes the nerve terminals of substance P, which is considered to be the neurotransmitter responsible for pain message transmission.\textsuperscript{[254]} Application of 0.025–0.075\% cream 2–4 times daily for 8 weeks may be very effective for chronic pain in diabetic neuropathy, post-herpetic neuralgia or nerve injury.\textsuperscript{[255,256]} It can also be helpful in phantom limb pain,\textsuperscript{[236]} post-mastectomy pain\textsuperscript{[257]} and in some cases of osteoarthritis.\textsuperscript{[258]} Severe burning at the application site limits its use and careful attention must be given not to get it in contact with eyes or mucosa. An assistant person or nurse should apply the cream to the feet of patients with diabetes mellitus. Continuous use is contraindicated as it may cause irreversible damage to the nerve terminations.

Mexiletine, clonidine and lidocaine are occasionally used for neuropathic pain, but don’t seem to be very effective. In most countries they are not approved for this indication, so extra care is needed when these drugs are used in the treatment of pain. In particular, their cardiac effects limit their use in the elderly.\textsuperscript{[236,259,260]}

Memantine, an NMDA antagonist, has not been shown to be effective in the treatment of neuropathic pain after amputation or surgery.\textsuperscript{[261,262]} While for continuous ketamine infusion there is evidence of analgesic effect,\textsuperscript{[263]} In the elderly, the central adverse effects (confusion, hallucination) inhibit its use. Recent studies have shown pain-reducing effects with dextromethorphan or amantadine in peripheral diabetic neuropathy.\textsuperscript{[264,265]}

Calcitonin is an endogenous hormone secreted by the C cells of the thyroid. It is involved in the regulation of calcium homeostasis. The mechanism of pain-reducing action has not been completely established, a central mechanism is presumed.\textsuperscript{[157,266]} It has proven to be effective in treatment of pain in osteoporosis, especially in vertebral fracture and phantom limb pain, however, its use in painful osteolytic metastasis is not helpful.\textsuperscript{[267-270]}

Bisphosphonate therapy is also useful in managing metastatic bone pain. Parenteral pamidronic acid 60–90mg once a month is best studied in the treatment of metastatic cancer pain or multiple myeloma.\textsuperscript{[161,271,272]} From their mechanism of action, other bisphosphonates (etidronic acid, risedronic acid, alendronic acid) could also be considered as potentially useful adjunctives in the therapy of bone pain from metastatic or osteoporotic origin.\textsuperscript{[273]} The oral administration route, with its need of upright position after ingestion, is sometimes difficult to manage and weekly administration of 70mg alendronic acid therefore offers advantages.

Systemic corticosteroids are indicated in the treatment of a variety of inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus. Particularly in temporal arteritis, their use is mandatory to prevent irreversible blindness and in polymyalgia rheumatica these provide rapid pain relief.\textsuperscript{[45]} Intra-articular injections of crystalloid corticosteroids should be considered for osteoarthritis, especially when a joint is painful and swollen.\textsuperscript{[274,275]} Intra-articular injections should be given under strictly aseptic conditions; complications are rare and include infection or joint injury.\textsuperscript{[276]} The injection can be repeated after 3 months.\textsuperscript{[45]}

Antipsychotics are frequently used in agitation, delirium or psychotic states in the elderly. In pain therapy they can help to reduce nausea caused by opioids while a specific analgesic action is not present for most antipsychotics.\textsuperscript{[230,235]} Olanzapine seems to be beneficial for patients with cancer pain associated with cognitive impairment or anxiety.\textsuperscript{[277]}

Antihistamines have been employed with some efficacy in a number of pain disorders,\textsuperscript{[230,278]} but some studies found neither analgesic nor relevant adjunctive action.\textsuperscript{[100,235]} Their sedative and anti-anxiety potential can be useful. Frequent drowsiness and anticholinergic adverse effects should be carefully considered.

Tetrahydrocannabinol is the most active component of cannabis, acting on cannabinoid and poss-
<table>
<thead>
<tr>
<th>Condition</th>
<th>Pharmacological therapy mild pain</th>
<th>Pharmacological therapy moderate-to-severe pain</th>
<th>Non-pharmacological therapy</th>
<th>Adjunctive therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>Paracetamol (acetaminophen), dipyridine (pyrazolone)</td>
<td>Try NSAIDs or add opioid (codeine, tramadol, tilidine/naloxone) with NSAID</td>
<td>Heat application, TENS, physiotherapy</td>
<td>Topical NSAID or capsaicin gel</td>
<td>Sometimes heat or ice therapy effective</td>
</tr>
<tr>
<td>Osteoarthritis with severe inflammation</td>
<td>NSAID (diclofenac, ibuprofen), COX-2 inhibitors</td>
<td>Add opioid [(codeine, tramadol, tilidine/naloxone) or [morphine, fentanyl, oxycodone]]</td>
<td>Ice application, TENS, physiotherapy</td>
<td>Topical NSAID or capsaicin gel</td>
<td>Intra-articular corticosteroid if other measures fail</td>
</tr>
<tr>
<td>Low back pain</td>
<td>Paracetamol, dipyridine or NSAID (diclofenac, ibuprofen), COX-2 inhibitors</td>
<td>Add opioid [(codeine, tramadol, tilidine/naloxone) or [especially in chronic conditions morphine, fentanyl, oxycodone)]/transdermal fentanyl and buprenorphine</td>
<td>Rest, physiotherapy, psychotherapy, TENS</td>
<td>Calcitonin with vertebral fractures, SSRIs sometimes effective, intradermal local anaesthetics</td>
<td>Assess for depression, therapy of osteoporosis if present</td>
</tr>
<tr>
<td>Pain in terminal disease</td>
<td>NSAIDs, COX-2 inhibitors, dipyridine, paracetamol plus opioid</td>
<td>NSAIDs, COX-2 inhibitors, dipyridine, paracetamol plus opioids plus adjunctive treatment</td>
<td>Cognitive-behavioural therapy, spiritual counselling, prayer</td>
<td>Adjunctives (tricyclic antidepressants, antipsychotics, SSRIs, THC) for anti-nausea and appetite-stimulating effects</td>
<td>Advise fixed timetable with long-acting opioids and addition of short-acting opioids for peaks of pain</td>
</tr>
<tr>
<td>Osteoporosis with fracture</td>
<td>NSAIDs, COX-2 inhibitors, dipyridine, paracetamol</td>
<td>Add opioid (oral or transdermal)</td>
<td>Physiotherapy, occupational therapy, isometric training, local heat, hip protectors</td>
<td>Bisphosphonates, calcitonin, calcium, vitamin D</td>
<td>Prevent fractures and falls</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>Tricyclic antidepressants (desipramine, nortriptyline), anticonvulsants (gabapentin, carbamazepine)</td>
<td>Add opioids; calcitonin, mexiletine or clonidine sometimes effective</td>
<td>Always try TENS, sympatholytic therapy and psychotherapy sometimes effective</td>
<td>Topical capsaicin sometimes effective, NMDA antagonists (ketamine) anecdotally found useful</td>
<td>Reduce pre-amputation, intra- and postoperative pain input</td>
</tr>
</tbody>
</table>

*Continued next page*
### Table III.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diabetic neuropathy</th>
<th>Trigeminal neuralgia</th>
<th>Visceral pain (i.e., renal, pancreatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain</td>
<td>Tricyclic antidepressants (desipramine, nortriptyline, amitriptyline)</td>
<td>Anticonvulsants (gabapentin, carbamazepine)</td>
<td>COX-2 = cyclo-oxygenase-2 inhibitor (e.g., celecoxib)</td>
</tr>
<tr>
<td>Moderate-to-severe pain</td>
<td>Captopril or ketamine, mexiletine or clonidine, sometimes effective</td>
<td>Phenytoin or baclofen can be tried</td>
<td>First causal therapy; then try dipryone, NSAIDs or piroxicam</td>
</tr>
<tr>
<td>Pharmacological therapy</td>
<td>Local opioid analgesia in the ganglion, operative decompression therapy, or percutaneous thermal ablation</td>
<td>Diagnostic ultrasonography or CT/ NMR, sometimes or local fluoroscopy; local thermotherapy useful</td>
<td>Antidepressants (fluoxetine)</td>
</tr>
<tr>
<td>Non-pharmacological therapy</td>
<td>Always try TENS, foot exercises and proper foot care</td>
<td>Antispasmodics (hyoscine or scopolamine)</td>
<td>TENS = transcutaneous electrical nerve stimulation; SSRI = selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>Levodopa in restless legs syndrome effective</td>
<td>Oropharyngeal counselling</td>
<td>THC = tetrahydrocannabinol</td>
</tr>
<tr>
<td>Comments</td>
<td>Always offer diabetes mellitus education, prevention of diabetic foot syndrome, basic diabetic foot care aimed at achieving normoglycaemia, initially pain can increase</td>
<td>Therapy is always a preventive therapy</td>
<td>An oily solution of 2.5% tetrahydrocannabinol can be tried in patients with decreased appetite and having pain to ameliorate mood, appetite and to reduce adverse effects of other analgesics. Analgesic potency is similar to codeine. Psychotropic adverse effects can occur that limit its use in the elderly.</td>
</tr>
</tbody>
</table>

#### 7. Specific Recommendations for Pain Management in the Elderly

Specific pain management recommendations for frequent non-malignant conditions in the elderly are given in Table III. These include both pharmacological and non-pharmacological strategies.

#### 8. Conclusion

Persistent non-malignant pain is common among older people. Significant proportions of these individuals do not receive appropriate assessment and treatment. The consequences of this in old age are numerous as pain often interferes with normal functioning. Depression, anxiety, decreased social activity, sleep disturbance and impaired ambulation are also associated with persistent pain.

Drug therapy is the most common treatment for pain control in older patients. The inadequate medical management is mainly as a result of the concerns regarding adverse effects. However, there is now a broad range of analgesics with a good safety profile and adjuvant drugs available and an adjustment to the individual needs and physical conditions is possible. Following the guidelines for appropriate drug use can help to minimise adverse effects. Whenever possible, non-pharmacological treatments should be combined with drug treatment.

Intense pain is not a normal part of aging and should not be accepted. Modern pain management strategies can substantially alleviate pain and may help to improve patient’s quality of life.
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