Management of cancer pain: ESMO Clinical Practice Guidelines

C. I. Ripamonti, E. Bandieri & F. Roila

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Incidence of pain

According to the World Health Organization (WHO), the incidence of cancer was 12,667,470 new cases in 2008 and, based on projections, it will be >15 million in 2020 [1]. Consistent with this, a systematic review of the literature, which investigated the prevalence of pain in different disease stages and types of cancer during the period 1966–2005[2], showed no difference in pain prevalence between patients during anticancer treatment and those in an advanced or terminal phase of the disease. In particular, pain prevalence was 64% in patients with metastatic, advanced or terminal phases of the disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment. Moreover, in the systematic review of the literature carried out by Deandrea et al. [3] on studies published from 1994 to 2007, nearly half of the cancer patients were undertreated, with a high variability across study designs and clinical settings. Recent studies conducted both in Italy and in Europe [4, 5] confirmed these data, showing that pain was present in all phases of cancer disease (early and metastatic) and was not adequately treated in a significant percentage of patients, ranging from 56 to 82.3%. In particular, Apolone et al. [6] evaluated prospectively the adequacy of analgesic care of cancer patients by means of the Pain Management Index (PMI) in 1802 valid cases of in- and outpatients with advanced/metastatic solid tumor enrolled in 110 centers specifically devoted to cancer and/or pain management (oncology/pain/palliative centers or hospices). The study showed that patients were still classified as potentially undertreated in 25.3% of the cases (range 9.8–55.3%). In contrast to the percentage of incidence of pain reported in hematological patients (5% with leukemia and 38% with lymphoma) in the past literature [7], a significant proportion of patients with lymphoma and leukemia may suffer from pain not only in the last months of life (83%) [4] but also at the time of diagnosis and during active therapies [8]. Based on these facts it is evident that millions of cancer patients still suffer from cancer-related pain.

Recommendation. The assessment and management of pain in cancer patients is of paramount importance in all stages of the disease; however, pain is still not adequately treated (expert and panel consensus).

Assessment of patients with pain

According to the literature, most patients with advanced cancer have at least two types of cancer-related pain which derive from a variety of etiologies [9, 10]. Sixty-nine per cent of patients rate their worst pain at a level that impaired their ability to function [11]. Table 1 shows the guidelines for a correct and complete assessment of the patient with pain. The proper and regular self-reporting assessment of pain with the help of validated assessment tools is the first step for an effective and individualized treatment. The most frequently used standardized scales [12] are reported in Figure 1 and are: visual analog scales (VAS), a verbal rating scale (VRS) and a numerical rating scale (NRS).

Recommendation. The intensity of pain and the treatment outcomes should be regularly assessed using (i) a visual analog scales (VAS), (ii) a verbal rating scale (VRS) or (iii) a numerical rating scale (NRS) [V, D].

Older age and the presence of limited communicative skills or of cognitive impairment such as during the last days of life makes the self-reporting of pain more difficult, although there is no evidence of clinical reductions in pain-related suffering. When cognitive deficits are severe, observation of pain-related behaviors and discomfort (i.e. facial expression, body movements, verbalization or vocalizations, changes in interpersonal interactions, changes in routine activity) is an alternative strategy for assessing the presence of pain (not its intensity) [13–16]. Different observational scales are available in the literature [15], but none of them is validated in different languages.
Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain (expert and panel consensus).

Psychosocial distress has to be assessed because it is strongly associated with cancer pain [17]. In fact psychosocial distress may amplify the perception of pain-related distress and, similarly, inadequately controlled pain may cause substantial psychological distress.

The assessment of all components of suffering such as psychosocial distress should be considered and evaluated [II, B].

principles of pain management

- Inform the patients about the possible onset of pain at any stage of the disease both during and after diagnostic interventions, in addition to as a consequence of cancer or anticancer treatments, and involve them in pain management. They have to be encouraged to communicate with the physician and/or the nurse about their suffering, the efficacy of therapy and any side effects, and not to consider the analgesic opioids as a therapeutic approach for dying patients [18], thus contributing to reduce opioidophobia. The patients’ involvement in pain management improves communication and has a beneficial effect on patients’ pain experience [19].

recommendation

Patients should be informed about pain and pain management and be encouraged to take an active role in their pain management [II, B].

- Prevent the onset of pain by means of the ‘by the clock’ administration, taking into account the half-life, bioavailability and duration of action of the different drugs.

recommendation

Analgesic for chronic pain should be prescribed on a regular basis and not on ‘as required’ schedule [V, D].

- Prescribe a therapy which is simple to be administered and easy to be managed by the patient himself and his family, especially when the patient is cared for at home. The oral route appears to be the most suitable to meet this requirement, and, if well tolerated, it must be considered as the preferred route of administration [20–24].

recommendation

The oral route of administration of the analgesic drugs should be advocated as the first choice [IV, C].

- Assess and treat the breakthrough pain (BTP) which is defined as a transitory exacerbation of pain that occurs in addition to an otherwise medically controlled stable pain [25, 26]. It is of sudden onset, occurs for short periods of time and is usually severe. The incidence of BTP has been estimated to be high (~20–80% depending on the setting) in various surveys [26, 27]. The differences reported are probably due to the different clinical settings analyzed and the different definitions of BTP used.

recommendation

Rescue dose of medications (as required) other than the regular basal therapy must be prescribed for breakthrough pain episodes [V, D].

- Tailor the dosage, the type and the route of drugs administered according to each patient’s needs. The type and the dose of the analgesic drugs is influenced by the intensity of pain (Table 2) and have to be promptly adjusted to reach a balance between pain relief and side effects. The rescue doses taken by the patients are an appropriate measure of the daily titration of the regular doses [25, 26]. An alternative route for opioid administration should be considered when oral

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Table 1. Guidelines for a correct assessment of the patient with pain

<table>
<thead>
<tr>
<th>1. Assess and re-assess the pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Causes, onset, type, site, duration, intensity, relief and temporal patterns of the pain</td>
</tr>
<tr>
<td>- Presence of the trigger factors and the signs and symptoms associated with the pain</td>
</tr>
<tr>
<td>- Use of analgesics and their efficacy and tolerability</td>
</tr>
<tr>
<td>2. Assess and re-assess the patient</td>
</tr>
<tr>
<td>- The clinical situation by means of a complete/specific physical examination and the specific radiological and/or biochemical investigations</td>
</tr>
<tr>
<td>- The presence of interference of pain with the patient’s daily activities, work, social life, sleep patterns, appetite, sexual functioning and mood</td>
</tr>
<tr>
<td>- The impact of the disease and the therapy on the physical, psychological and social conditions</td>
</tr>
<tr>
<td>- The presence of a caregiver, the psychological status, the degree of awareness of the disease, anxiety and depression and suicidal ideation, his/her social environment, quality of life, spiritual concerns/needs</td>
</tr>
<tr>
<td>- The presence and intensity of signs, physical and/or emotional symptoms associated with cancer pain syndromes</td>
</tr>
<tr>
<td>- The functional status</td>
</tr>
<tr>
<td>- The presence of opioidophobia</td>
</tr>
<tr>
<td>3. Assess and re-assess your ability to inform and to communicate with the patient and the family</td>
</tr>
<tr>
<td>- Take time to spend with the patient and the family to understand their needs</td>
</tr>
</tbody>
</table>

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Validated assessment tools for the assessment of pain

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
</tr>
<tr>
<td>0 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
</tr>
<tr>
<td>Very mild</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Very severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numerical scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Figure 1. Validated and most frequently used pain assessment tools.

**recommendation** Observation of pain-related behaviors and discomfort is indicated in patients with cognitive impairment to assess the presence of pain (expert and panel consensus).

Psychosocial distress has to be assessed because it is strongly associated with cancer pain [17]. In fact psychosocial distress may amplify the perception of pain-related distress and, similarly, inadequately controlled pain may cause substantial psychological distress.

**recommendation** The assessment of all components of suffering such as psychosocial distress should be considered and evaluated [II, B].
annals of oncology

Table 2. Categorization of pain and appropriate analgesia

<table>
<thead>
<tr>
<th>WHO analgesic ladder step</th>
<th>Score on NRS</th>
<th>Analgesics of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mild pain)</td>
<td>&lt;3 out of 10</td>
<td>Paracetamol or NSAIDs</td>
</tr>
<tr>
<td>(mild to moderate pain)</td>
<td>3-6 out of 10</td>
<td>Weak opioids ± paracetamol or NSAIDs</td>
</tr>
<tr>
<td>(moderate to severe pain)</td>
<td>&gt;6 out of 10</td>
<td>Strong opioids + paracetamol NSAIDs</td>
</tr>
</tbody>
</table>

*Score on NRS according to references 24, 29, 30.

NRS, numerical rating scale; NSAIDs, non-inflammatory drugs; WHO, World Health Organization.

administration is not possible because of severe vomiting, bowel obstruction, severe dysphagia or severe confusion, as well as in the presence of poor pain control, which requires rapid dose escalation, and/or in the presence of oral opioid-related adverse effects.

pain management

In 1986, the WHO proposed a strategy for cancer pain management based on a sequential three-step analgesic ladder from non-opioids to weak opioids to strong opioids according to pain intensity [28]. Twenty years after the first edition [20], the WHO cancer pain relief program remains the referral point for pain management. According to WHO guidelines, opioid analgesics are the mainstay of analgesic therapy and are classified according to their ability to control pain from mild to mild–moderate to moderate–severe intensity. Such pain intensity may be scored on an NRS as reported in Table 2 [24, 29, 30].

However, the intensity of pain is frequently reported as mild, moderate and severe and scored on an NRS respectively as ≤4, from 5 to 6, and ≥7 [31].

Opioid analgesics may be combined with non-opioid drugs such as paracetamol or with non-steroidal anti-inflammatory drugs (NSAIDs) and with adjuvant drugs [32, 33].

recommendation

The analgesic treatment should start with drugs indicated by the WHO analgesic ladder appropriate for the severity of pain [II, IB].

Pain should already be managed during the diagnostic evaluation. Most cancer patients can attain satisfactory relief of pain through an approach that incorporates primary antitumor treatments, systemic analgesic therapy and other non-invasive techniques such as psychological or rehabilitative interventions.

treatment of mild pain

For the treatment of mild pain non-opioid analgesics such as acetaminophen/paracetamol or an NSAID are widely used (Table 3).

NSAIDs are superior to placebo in relieving cancer pain in single dose studies. There is no evidence to support superior safety or efficacy of one NSAID over any other [34]. In a randomized clinical trial (RCT) carried out in a small sample of cancer patients on a strong opioid regimen, paracetamol improved pain and well-being [35]. However, these results have not been confirmed by other studies.

recommendation

Paracetamol and/or a non-steroidal anti-inflammatory drug are effective for treating mild pain [I, A].

Paracetamol and NSAIDS are universally accepted as part of the treatment of cancer pain at any stage of the WHO analgesic ladder. The long-term use of NSAIDS or a cyclo-oxygenase-2 (COX-2) selective inhibitor has to be carefully monitored and reviewed periodically [36] because they can provoke severe toxicity such as: gastrointestinal bleeding, platelet dysfunction and renal failure. COX-2 selective inhibitors may increase the risk of thrombotic cardiovascular adverse reactions [37] and do no protect from renal failure.

Not all of the described drugs are available in all countries.

recommendation

Paracetamol and/or a non-steroidal anti-inflammatory drug are effective for treating all intensities of pain, at least in the short term and unless contraindicated [I, A].

recommendation

Paracetamol and/or a non-steroidal anti-inflammatory drug are effective for treating mild pain [I, A].

For mild to moderate pain, weak opioids such as codeine, dihydrocodeine, tramadol or propoxyphene (Table 4).

The use of drugs of the second step of the WHO ladder has several controversial aspects. The first criticism concerns the absence of a definitive proof of efficacy of weak opioids: in a meta-analysis of data reported from clinical RCTs [38] no significant difference was found in the effectiveness between non-opioid analgesics alone, and the combination of these with weak opioids. The available studies do not even demonstrate a clear difference in the effectiveness of the drugs between the first and the second step [39]. Uncontrolled studies also show that the effectiveness of the second step of the WHO ladder has a time limit of 30–40 days for most patients and that the shift to the third step is mainly due to insufficient analgesia achieved, rather than to adverse effects [40]. A further limitation in the use of weak opioids is represented by the ‘ceiling effect’, for which more than a certain threshold of dose cannot increase the effectiveness of the drug but only influence the appearance of side effects. Many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favor of the early use of morphine at low doses. The few studies on this specific topic [41–43], though suggestive, have reported inconclusive results due both to the low number and representativeness of the patients sample studied and to the relatively low statistical power.

An RCT is urgently needed to address the relevant issue of the role of WHO step II.

recommendation

For moderate to severe pain, weak opioids such as codeine, tramadol and dihydrocodeine should be given in combination with non-opioid analgesics [III, C].

As an alternative to weak opioids, consider low doses of strong opioids in combination with non-opioid analgesics [III, C].

Table 2. Categorization of pain and appropriate analgesia

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<tr>
<td>(mild to moderate pain)</td>
<td>3-6 out of 10</td>
<td>Weak opioids ± paracetamol or NSAIDs</td>
</tr>
<tr>
<td>(moderate to severe pain)</td>
<td>&gt;6 out of 10</td>
<td>Strong opioids ± paracetamol NSAIDs</td>
</tr>
</tbody>
</table>

*Score on NRS according to references 24, 29, 30.
treatment of moderate–severe pain

Strong opioids (Table 5) are the mainstay of analgesic therapy in treating moderate–severe cancer-related pain. In some countries, pain relief is hampered by a lack of availability or barriers to accessibility to opioid analgesics [44]. Morphine, methadone, oxycodone, hydromorphone, fentanyl, alfentanil, buprenorphine, heroin, levorphanol and oxymorphone are the most widely used strong opioids in Europe [33, 45]. In the last years in some countries, the consumption of oxycodone and the use of patches of fentanyl and buprenorphine has been increasing [46]. However, there is no evidence from high quality comparative studies that other opioids are superior to morphine in terms of efficacy and tolerability.

In many countries, since 1977, oral morphine has been used in Hospices and Palliative Care Units as the drug of choice for the management of chronic cancer pain of moderate to severe intensity because it provides effective pain relief, is widely tolerated, is simple to be administered and is cheap. Moreover, morphine is the only opioid analgesic considered in the WHO essential drug list for adults and children with pain [47].

recommendation

The opioid of first choice for moderate to severe cancer pain is oral morphine [IV, D].

Although the oral route of administration is advocated, the patients presenting with severe pain who needs urgent relief should be treated and titrated with parenteral opioids, usually administered by the subcutaneous (s.c.) or intravenous (i.v.) route.

If given parenterally, the equivalent dose is one-third of that of the oral medication. The relative potency ratio of oral to parenteral (s.c. or i.v.) morphine (not subject to ‘first-pass’ metabolism) [48, 49] might vary according to the circumstances in which morphine is used and among individual patients. When converting from oral to parenteral morphine, the dose should be divided by three to get a roughly equianalgesic effect, but upward or downward adjustment of the dose may then be required [50].

recommendation

The average relative potency ratio of oral to intravenous morphine is between 1:2 and 1:3 [II, A].

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Table 3. Selected non-opioid analgesics for mild pain (WHO step I)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely available forms and strengths</th>
<th>Time to onset (min)</th>
<th>Caution</th>
<th>Maximal daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>Tablets, suppositories 500–1000 mg</td>
<td>15–30</td>
<td>Hepatotoxicity</td>
<td>4 × 1000 mg</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Tablets 500–1000 mg</td>
<td>15–30</td>
<td>GI toxicity, allergy, platelet inhibition</td>
<td>3 × 1000 mg</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Tablets 200–400–600 mg; tablets 800 mg modified release; topical gels</td>
<td>15–30; 120+</td>
<td>GI and renal toxicity</td>
<td>4 × 600 mg; 3 × 800 mg modified release</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tablets 25–75 mg; tablets 100–150–200 mg modified release</td>
<td>30+</td>
<td>GI and renal toxicity</td>
<td>4 × 75 mg; 2 × 200 mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Tablets 25–50–75 mg; tablets 100 mg modified release</td>
<td>30–120</td>
<td>GI and renal toxicity</td>
<td>4 × 50 mg; 2 × 100 mg</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Capsules 250–500 mg</td>
<td>30+</td>
<td>GI and renal toxicity</td>
<td>4 × 500 mg</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Tablets 250–375–500 mg</td>
<td>30+</td>
<td>GI and renal toxicity</td>
<td>2 × 500 mg</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; WHO, World Health Organization.

Table 4. Comparison of selected opioids for mild to moderate pain (WHO step II)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely available forms and strengths</th>
<th>Relative effectiveness compared with oral morphine</th>
<th>Duration of effectiveness (h)</th>
<th>Maximal daily dose without pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrocodeine</td>
<td>Modified-release tablets 60–90–120 mg Tablet 15–30–60 mg</td>
<td>0.17</td>
<td>12</td>
<td>240 mg; 60–120 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>Tablets 60–90–120 mg</td>
<td>0.17</td>
<td>12</td>
<td>240 mg; 60–120 mg</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Drops 100 mg/ml; capsules 50 mg</td>
<td>0.1–0.2</td>
<td>2–4</td>
<td>400 mg; 50–100 mg</td>
</tr>
<tr>
<td></td>
<td>Modified-release tablets 100–150–200 mg</td>
<td>0.1–0.2</td>
<td>12</td>
<td>400 mg; 50–100 mg</td>
</tr>
</tbody>
</table>

WHO, World Health Organization.
Table 5. Comparison of selected opioids for moderate to severe pain (WHO step III)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Route</th>
<th>Relative effectiveness compared with oral morphine&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Maximal daily dose</th>
<th>Starting dose without pretreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>Oral</td>
<td>1</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>i.v.</td>
<td>3</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5–10 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oral</td>
<td>1.5–2</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral</td>
<td>7.5</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 mg</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>TTS</td>
<td>+ 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 µg/h&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Oral</td>
<td>75</td>
<td>4 mg</td>
<td>0.4 mg</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>100</td>
<td>3 mg</td>
<td>0.3–0.6 mg</td>
</tr>
<tr>
<td>Buprenorphine transdermal</td>
<td>TTS</td>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>140 µg/h</td>
<td>17.5–35 µg/h</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral</td>
<td>4–8–12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No upper limit&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 mg</td>
</tr>
<tr>
<td>Nicomorphine</td>
<td>Oral</td>
<td>1</td>
<td>20 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Nicomorphine</td>
<td>i.v.</td>
<td>3</td>
<td>20 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup>The relative effectiveness varies considerably in the published literature and among individual patients. Switching to another opioid should therefore be done cautiously with a dose reduction of the newly prescribed opioid.

<sup>b</sup>The maximal dose depends on tachyphylaxis.

<sup>c</sup>Calculated with conversion from mg/day to µg/h.

<sup>d</sup>Not usually used as first opioid (the 12 µg/h dose corresponds to about 30 mg of oral morphine sulfate daily).

<sup>e</sup>Factor 4 for daily morphine doses <90 mg, factor 8 for doses 90–300 mg, and 12 for >300 mg.

WHO, World Health Organization; i.v. intravenous.

The average relative potency ratio of oral to subcutaneous morphine is between 1:2 and 1:3 [IV, C].

Only a few selected patients (1–2%) with cancer pain, refractory to all conventional strategies and/or dose-limiting analgesic-related side effects, require spinal analgesia [51]. Based on the findings of Myers, Smith and Kalso [52–54] and the documented bias of the investigation of Smith et al. [55], it is evident that the role of intraspinal opioids has not been established, and well-designed, independently funded clinical trials are required. Hydromorphone or oxycodone, in both immediate-release and modified-release formulations for oral administration, are effective alternatives to morphine.

Transdermal fentanyl and transdermal buprenorphine are best reserved for patients whose opioid requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, patients with poor tolerance of morphine and patients with poor compliance. Although not recommended in the NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain [21] because it is a partial agonist, buprenorphine has a role in the analgesic therapy of patients with renal impairment and undergoing hemodialysis treatment [56, 57] where no drug reduction is necessary, buprenorphine being mainly converted in the liver to norbuprenorphine (a metabolite 40 times less potent than the parent compound). Methadone is a valid alternative but, because of marked interindividual differences in its plasma half-life and duration of action, it is still considered as a drug which should be initiated by physicians with experience and expertise in its use. Strong opioids may be combined with ongoing use of a non-opioid analgesic (step 1).

**Recommendation**

In the presence of renal impairment all opioids should be used with caution and at reduced doses and frequency [IV, C].

Buprenorphine is the safest opioid of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min) [IV, C].

Opioid switching is a practice used to improve pain relief and/or drug tolerability. Although there is no high quality evidence to support this practice, a switch to an alternative opioid is to be considered in clinical practice [58]. This approach requires familiarity with equianalgesic doses of the different opioids [33].

**Scheduling and Titration**

Opioid doses should be titrated to take effect as rapidly as possible. Titration is a process for which the dose of the opioid is speedily modified to obtain the tailored dose which provides adequate relief of pain with an acceptable degree of side effects.

Normal release morphine has a short half-life and is indicated during the titration phase and for treating BTP episodes. I.v. titration is indicated in patients with severe pain (Table 6) [59]. All patients should receive round-the-clock dosing with provision of a 'breakthrough dose' to manage transient exacerbations of pain. The 'breakthrough dose' is usually equivalent to 10–15% of the total daily dose. If more than four 'breakthrough doses' per day are necessary, the baseline opioid treatment with a slow-release formulation has to be adapted. Opioids with a rapid onset and short duration are preferred for breakthrough doses. After the titration period slow-release opioids are indicated.

**Recommendation**

Individual titration of dosages by means of normal release morphine administered every 4 h plus rescue doses (up to hourly) for BTP are recommended in clinical practice [IV, C].

The regular dose of slow-release opioids can then be adjusted to take into account the total amount of rescue morphine [IV, C].
management of opioid side effects

Many patients develop adverse effects such as constipation, nausea, vomiting, urinary retention, pruritus and central nervous system (CNS) toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and—rarely—opioid-induced hyperalgesia/allodynia). In some cases a reduction in opioid dose may alleviate refractory side effects. This may be achieved by using a co-analgesic or an alternative approach such as a nerve block or radiotherapy. Other strategies include the continued use of antiemetics for nausea, laxatives for constipation, major tranquillizers for confusion, and psychostimulants for drowsiness. However, since some of the side effects may be caused by accumulation of toxic metabolites, switching to another opioid agonist and/or another route may allow titration to adequate analgesia without the same disabling effects. This is especially true for symptoms of CNS toxicity such as opioid-induced hyperalgesia/allodynia and myoclonic jerks [60]. Naloxone is a short-acting opioid antagonist for i.v. use able to revert symptoms of accidental severe opioid overdose.

radiotherapy

Radiotherapy has specific and critical efficacy in providing pain relief caused by bone metastases. Radiotherapy also has a role in tumors compressing nerve structures and cerebral metastases. A systematic review [61] on the use of radiotherapy for bone pain showed complete pain relief at 1 month in 27% of the patients, and at least 50% relief in an additional 42% of the patients at any time in the trials included.

The radioisotope treatment has also been investigated in a systematic review [62]; the results showed only weak evidence of a small beneficial effect on pain control in the short and medium term (1–6 months), with no modification of the analgesics used. A few RCTs, involving small numbers, have shown that radioisotopes can relieve bone pain in patients with breast cancer [63] and lung cancer [64], while inconsistent results were produced in patients with hormone-refractory prostate cancer [65].

recommendation

All patients with pain from bone metastases which is proving difficult to be controlled by pharmacological therapy should be evaluated by a clinical oncologist for consideration of external beam radiotherapy or radioisotope treatment [II, B].

bisphosphonates and bone pain

Bisphosphonates (BPs) form part of the standard therapy for hypocalcemia and the prevention of skeletal-related events in some cancers. There is sufficient evidence supporting the analgesic efficacy of BPs in patients with bone pain due to bone metastases [66]. However, the prescription of BPs should not be considered as an alternative to analgesic treatment and their administration should be started after preventive dental

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**Table 6.** Intravenous titration (dose finding) with morphine for severe cancer pain (Harris et al. [59]).

<table>
<thead>
<tr>
<th>Study design and patient population</th>
<th>Initial morphine dosage and route</th>
<th>Subsequent dosage and route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT.</td>
<td>i.v. group:</td>
<td>i.v. group:</td>
<td>% of patients achieving satisfactory pain relief:</td>
</tr>
<tr>
<td>62 strong opioid-naive inpatients pain intensity</td>
<td>1.5 mg bolus every 10 min until pain relief (or adverse effects).</td>
<td>Oral IR morphine 4 hourly, on the basis of the previous i.v. requirements. i.v.: p.o. conversion 1:1. Rescue dose: the same dose every 1 h max. Oral group: follow the same scheme</td>
<td>after 1 h: i.v. group, 84%; oral group, 25% (P &lt;0.001) after 12 h: i.v. group 97%; oral group 76% (P &lt;0.001) after 24 h: i.v. group and oral group similar.</td>
</tr>
<tr>
<td>NRS ≥5 Patients randomized to receive i.v. morphine (n = 31) or oral IR morphine (n = 31)</td>
<td>Oral group: IR morphine 5 mg every 4 h in opioid-naive patients. 10 mg in patients on weak opioids. Rescue dose: the same dose every 1 h max.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IR, immediate release, i.v., intravenous; NRS, numerical rating scale; p.o., per os; RCT, randomized controlled trial.
Opioid analgesics may be combined with tricyclic antidepressants with various different anticonvulsants [72]. Gabapentin in the management of pain [71] and the other dealing with anticonvulsant drugs in neuropathic pain, one dealing with specific systematic reviews have been identified on the role of antidepressants and anticonvulsant drugs are effective in the management of neuropathic pain [69, 71, 72] even if the number needed to treat (NNT) for these drugs is between 3 and 5. Two specific systematic reviews have been identified on the role of anticonvulsant drugs in neuropathic pain, one dealing with gabapentin in the management of pain [71] and the other dealing with various different anticonvulsants [72].

In cancer patients with neuropathic pain, non-opioid and opioid analgesics may be combined with tricyclic antidepressant drugs or anticonvulsants (Table 7). The efficacy and tolerability of the therapy have to be monitored over time. Steroids should be considered in the case of nerve compression. There is evidence in adults that i.v. lidocaine and its oral analog mexiletine are more effective than placebo in decreasing neuropathic pain and can relieve pain in selected patients [73].

**Table 7.** Selected adjuvant drugs for neuropathic pain

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely available forms and strengths (mg)</th>
<th>Activity</th>
<th>Sedation</th>
<th>Range of daily doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Tablets 25–50</td>
<td>Antidepressive</td>
<td>+++</td>
<td>50–200</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tablets 10–75</td>
<td>Antidepressive</td>
<td>(+)</td>
<td>50–200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tablets 10–25</td>
<td>Antidepressive</td>
<td>+</td>
<td>50–225</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Tablets 20</td>
<td>Antidepressive</td>
<td>+</td>
<td>20–80</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Tablets 30–60</td>
<td>Antidepressive</td>
<td>+</td>
<td>60–120</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tablets 200–400</td>
<td>Antiepileptic</td>
<td>+</td>
<td>400–1600</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tablets 200–300–400–800</td>
<td>Antiepileptic</td>
<td>++</td>
<td>900–3600</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Tablets 25–50–75–100–150–200–300 mg</td>
<td>Antiepileptic</td>
<td>+</td>
<td>150–600</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Drops, tablets, vials</td>
<td>Neuroleptic</td>
<td>+</td>
<td>3–20</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Drops, tablets, suppositories, vials</td>
<td>Neuroleptic</td>
<td>vials</td>
<td>25–200</td>
</tr>
</tbody>
</table>

Usually the lowest doses of antidepressants and neuroleptics are sufficient as an adjunct to opioids unless severe depression or major psychosis has to be treated with higher doses as appropriate.

**recommendation**

Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of patients with/without pain due to metastatic bone disease [II, B]. Preventive dental measures are necessary before starting bisphosphonate administration [III, A].

**treatment of resistant and neuropathic pain**

Some patients, whose pain remains inadequately relieved, may benefit from invasive anesthetic or neurosurgical treatments. Limited evidence supports the use of subanesthetic doses of ketamine, an N-methyl-D-aspartate (NMDA) antagonist, in intractable pain. Neuropathic pain, either caused by tumor infiltration or due to paraneoplastic or treatment-induced polyneuropathy, may not be adequately controlled by opioids alone. Long-lasting and neuropathic pain may cause psychological problems that should be specifically addressed. Few studies have been identified which were carried out directly on patients with cancer pain. Evidence from studies in patients without cancer has been reviewed as the pathological mechanism of neuropathic pain involved is believed to be the same. There is evidence from systematic reviews [69, 70] that both tricyclic antidepressants and anticonvulsant drugs are effective in the management of neuropathic pain [69, 71, 72] even if the number needed to treat (NNT) for these drugs is between 3 and 5. Two specific systematic reviews have been identified on the role of anticonvulsant drugs in neuropathic pain, one dealing with gabapentin in the management of pain [71] and the other dealing with various different anticonvulsants [72].

In cancer patients with neuropathic pain, non-opioid and opioid analgesics may be combined with tricyclic antidepressant drugs or anticonvulsants (Table 7). The efficacy and tolerability of the therapy have to be monitored over time. Steroids should be considered in the case of nerve compression. There is evidence in adults that i.v. lidocaine and its oral analog mexiletine are more effective than placebo in decreasing neuropathic pain and can relieve pain in selected patients [73].

**refractory pain at the end of life**

Recent data suggest that 53–70% of patients with cancer-related pain require an alternative route for opioid administration, months and hours before death [74, 75]. On some occasions, as patients are nearing death, pain is perceived to be ‘refractory’. In deciding that a pain is refractory, the clinician must perceive that the further application of standard interventions is either: (i) incapable of providing adequate relief; (ii) associated with excessive and intolerable acute or chronic morbidity; or (iii) unlikely to provide relief, so that other interventional approaches may be necessary to control pain. In this situation, sedation may be the only therapeutic option capable of providing adequate relief. The justification of sedation in this setting is that it is an appropriate and proportionate goal. However, before administering sedative drugs, all the possible causes of ‘suffering’ must be carefully assessed and evaluated by means of a multidisciplinary specialist approach which also includes a psychiatric, psychologist and pastoral care personnel. Commonly used agents include opioids, neuroleptics, benzodiazepines, barbiturates and propofol. Irrespective of the agent or agents selected, administration initially requires dose titration to achieve adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of the effect. A continuous assessment of the suffering of the patient should be performed during the sedation process.
note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature


