Management of cancer pain: ESMO Clinical Practice Guidelines

L. Jost1 & F. Roila2
On behalf of the ESMO Guidelines Working Group*

1Department of Oncology, Kantonsspital, Bruderholz, Switzerland; 2Department of Medical Oncology, S. Maria Hospital, Terni, Italy

incidence of pain

Over 80% of cancer patients with advanced metastatic disease suffer pain caused mostly by direct tumour infiltration. Pain undermines quality of life considerably and is a clinically important indicator of tumour progression. Cancer pain may be acute or chronic and should be addressed accordingly. Approximately 20% of pain in cancer patients may be attributed to the effects of surgery, radiotherapy or chemotherapy.

assessment and management

All patients should be evaluated for the presence of pain at every visit. Pain severity is best assessed by patient self-report and may be aided by visual analogue scales (VASs), numerical rated scales (NRSs) and/or verbal rated scales (VRSs). The extent of diagnostic investigation must be appropriate to the patient’s general status and the goals of care. Pain should already be managed during the diagnostic evaluation. Most cancer patients can attain satisfactory relief of pain through an approach that incorporates primary antitumour treatments, systemic analgesic therapy and other non-invasive techniques such as psychological or rehabilitative interventions. Stepwise escalation of analgesic therapy should usually follow the ‘pain ladder’ as described by the World Health Organization (WHO).

treatment of mild pain (WHO step I analgesics)

Mild pain (NRS: 1–4) is treated with non-opioid analgesics such as acetaminophen/paracetamol or a non-steroidal anti-inflammatory drug (NSAID) (Table 1). When NSAIDs are used over a prolonged period gastric protection is recommended. Caution and vigilance are required when using potentially nephrotoxic NSAIDs and when using these medications in patients at risk of bleeding.

treatment of moderate pain (WHO step II analgesics)

Traditionally, patients with moderate pain (NRS: 5–7) have been treated with a combination product containing acetaminophen, aspirin or an NSAID plus a weak immediate-release opioid such as codeine, dihydrocodeine, tramadol or propoxyphene or a strong opioid at low doses such as morphine or oxycodone (Table 2). The doses of these combination products can be increased until their maximum dose is attained (e.g. 4000 mg of acetaminophen and 240 mg of codeine). Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled release formulations of codeine, dihydrocodeine, tramadol, morphine and oxycodone in dosages appropriate for moderate pain. Additional options include low-dose formulations of transdermal fentanyl and of transdermal buprenorphine.

treatment of severe pain (WHO step III analgesics)

Morphine is most commonly used in severe pain (NRS: 8–10). Oral administration is the preferred route. If given parenterally, the equivalent dose is one-third of the oral medication. Hydromorphone or oxycodone, in both immediate-release and modified-release formulations for oral administration are effective alternatives to oral 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 to morphine and patients with poor compliance. Earlier worries regarding an inferior equipotency ratio of buprenorphine to oral morphine or of a ceiling effect and partial antagonistic effects of buprenorphine as compared with fentanyl have not been substantiated by newer publications.

Methadone is a valid alternative but may be more complicated to use because of marked inter-individual differences in its plasma half-life and duration of action. Methadone use 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). Patients presenting with severe pain that needs urgent relief should be treated with parenteral opioids, usually administered by the subcutaneous (s.c.) or
intravenous (i.v.) route. Intramuscular injections are painful and have no pharmacokinetic advantage.

**scheduling and titration**

Opioid doses should be titrated to take effect as rapidly as possible. 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.

**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 like opioid-induced hyperalgesia/allodynia and myoclonic jerks. This approach requires familiarity with equianalgesic doses of the different opioids (Table 3).

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 the relief of pain caused by bone metastases, tumours compressing neural structures and cerebral metastases. It is essential for managing radicular pain.

**surgery and other interventions**

Surgery may have a specific and critical efficacy in the relief of pain caused by impending or evident fractures. Surgery or

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**Table 1.** Selected non-opioid analgesics (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 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Tablets, suppositories 500–1000 mg</td>
<td>15–30</td>
<td>Hepatotoxicity</td>
<td>4–6 × 1000</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</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; 3 × 800 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; 2 × 200</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; 2 × 100</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</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</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; WHO, World Health Organization.

**Table 2.** Comparison of selected opioids for mild to moderate pain (WHO level 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 (mg)</th>
<th>Starting dose without pretreatment (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydrocodeine</td>
<td>Modified release tablets 60–90–120 mg</td>
<td>0.17</td>
<td>12</td>
<td>240</td>
<td>60–120</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</td>
<td>50–100</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</td>
<td>50–100</td>
</tr>
</tbody>
</table>

WHO, World Health Organization.
other interventional approaches may be necessary to control pain caused by obstruction of hollow organs.

**treatment of resistant and neuropathic pain**

Some patients, whose pain remains inadequately relieved, may benefit from invasive anaesthetic or neurosurgical treatments. Limited evidence supports the use of subanaesthetic doses of ketamine, an N-methyl-D-aspartate (NMDA) antagonist, in intractable pain.

Neuropathic pain either caused by tumour 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.

**Table 3.** Comparison of selected opioids for moderate to severe pain (WHO step III: may be combined with step I medication)

<table>
<thead>
<tr>
<th>Substance 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 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 parenteral</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 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 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>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 oral</td>
<td>75</td>
<td>4 mg</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Buprenorphine intravenous</td>
<td>100</td>
<td>3 mg</td>
<td>0.3–0.6 mg</td>
</tr>
<tr>
<td>Buprenorphine transdermal</td>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>140 µg/h</td>
<td>17.5–35 µg/h</td>
</tr>
<tr>
<td>Methadone 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 oral</td>
<td>1</td>
<td>20 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Nicomorphine 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 published literature and between 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 30–60 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.

**Table 4.** Selected co-analgesics for neuropathic pain

<table>
<thead>
<tr>
<th>Substance</th>
<th>Widely available forms and strengths</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 mg</td>
<td>Antidepressive</td>
<td>+++</td>
<td>50–200</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Tablets 10–75 mg</td>
<td>Antidepressive</td>
<td>(+)</td>
<td>50–200</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Tablets 10–25 mg</td>
<td>Antidepressive</td>
<td>+</td>
<td>50–225</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Tablets 20 mg</td>
<td>Antidepressive</td>
<td>+</td>
<td>20–80</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>++</td>
<td>25–200</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tablets 200–400 mg</td>
<td>Antiepileptic</td>
<td>+</td>
<td>400–1600</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tablets 200–300–400–800 mg</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>
</tbody>
</table>

Non-opioid and opioid analgesics may be combined with antidepressive or neuroleptic psychoactive drugs or antiepileptic drugs in the case of neuropathic pain (Table 4). Steroids should be considered in case of nerve compression. There is sufficient evidence for use of bisphosphonates for refractory bone pain but not for general use as first-line therapy of bone pain.

**refractory pain at the end of life**

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
within a tolerable time frame. 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
goal appropriate and proportionate. 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 effect.

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