

Management of cancer pain: ESMO Clinical Recommendations

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incidence of pain

Over 80% of cancer patients with advanced metastatic disease suffer pain caused mostly by direct tumor infiltration. Pain undermines quality of life considerably and is a clinically important indicator of tumor 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 (VAS), numerical rated scales (NRS) and/or verbal rated scales (VRS). 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 anti-tumor treatments, systemic analgesic therapy and other non-invasive techniques such as psychological or rehabilitative interventions. Step-wise 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 is 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

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Table 1. Selected non-opioid analgesics (WHO step I)

Substance	Widely available forms and strengths	Time to onset (min)	Caution	Maximal daily dose (mg)
Acetaminophen (paracetamol)	Tablets, suppositories 500–1000 mg	15–30	Hepatotoxicity	4–6 × 1000
Acetylsalicylic acid	Tablets 500–1000 mg	15–30	GI toxicity, allergy, platelet inhibition	3 × 1000
Ibuprofen	Tablets 200–400–600 mg; tablets 800 mg modified release; topical gels	15–30 + 120	GI and renal toxicity	4 × 600; 3 × 800 modified release
Ketoprofen	Tablets 25–75 mg; tablets 100–150–200 mg modified release	+ 30	GI and renal toxicity	4 × 75; 2 × 200
Diclofenac	Tablets 25–50–75 mg; tablets 100 mg modified release	30–120	GI and renal toxicity	4 × 50; 2 × 100
Mefenamic acid	Capsules 250–500 mg	+ 30	GI and renal toxicity	4 × 500
Naproxen	Tablets 250–375–500 mg	+ 30	GI and renal toxicity	2 × 500

GI, gastrointestinal; WHO, World Health Organization.

Table 2. Comparison of selected opioids for mild to moderate pain (WHO level II)

Substance	Widely available forms and strengths	Relative effectiveness compared with oral morphine	Duration of effectiveness (h)	Maximal daily dose (mg)	Starting dose without pretreatment (mg)
Dihydrocodeine	Modified release tablets 60–90–120 mg	0.17	12	240	60–120
Tramadol	Drops 100 mg/ml, capsules 50 mg	0.1–0.2	2–4	400	50–100
	Modified release tablets 100–150–200 mg	0.1–0.2	12	400	50–100

WHO, World Health Organization.

opioids, usually administered by the s.c. or 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 around 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, tumors 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 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 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 caused either 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.

Non-opioid and opioid analgesics may be combined with antidepressive or neuroleptic psychoactive drugs or anti-epileptic 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 are 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

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

Substance route	Relative effectiveness compared with oral morphine ^a	Maximal daily dose	Starting dose without pretreatment
Morphine sulfate oral	1	no upper limit ^b	20–40 mg
Morphine parenteral	3	no upper limit ^b	5–10 mg
Oxycodone oral	1.5–2	no upper limit ^b	20 mg
Hydromorphone oral	7.5	no upper limit ^b	8 mg
Fentanyl transdermal	+4 ^c	no upper limit ^b	12 µg/h ^d
Buprenorphine oral	75	4 mg	0.4 mg
Buprenorphine intravenous	100	3 mg	0.3–0.6 mg
Buprenorphine transdermal	+4 ^c	140 µg/h	17.5–35 µg/h
Methadone oral	4–8–12 ^c	no upper limit ^b	10 mg
Nicomorphine oral	1	20 mg	5 mg
Nicomorphine i.v.	3	20 mg	5 mg

^aThe 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.

^bThe maximal dose depends on tachyphylaxis.

^cCalculated with conversion from mg/day to µg/h.

^dNot usually used as first opioid (the 12 µg/h dose corresponds to 30–60 mg of oral morphine sulfate daily).

^eFactor 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

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

adequate relief, followed subsequently by provision of ongoing therapy to ensure maintenance of effect.

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

1. Caraceni A, Cherny N, Fainsinger R et al. The Steering Committee of the EAPC Research Network. Pain measurement tools and methods in clinical research in palliative care: recommendations of an expert working group of the European Association of Palliative Care. *J Pain Symptom Manage* 2002; 23: 239–255.
2. Mercadante S, Radbruch L, Caraceni A et al. Episodic (breakthrough) pain. Consensus Conference of an expert working group of the European Association for Palliative Care. *Cancer* 2002; 94: 832–839.
3. Fallon M, Hanks G, Cherny N. Principles of control of cancer pain. *BMJ* 2006; 332: 1022–1024.
4. Cherny NI. How to deal with difficult pain problems. *Ann Oncol* 2005; 16 (Suppl 2): ii79–87.
5. Wool MS, Mor V. A multidimensional model for understanding cancer pain. *Cancer Invest* 2005; 23: 727–734.
6. Quigley C. The role of opioids in cancer pain. *BMJ* 2005; 331: 825–829.
7. Cherny NI. The pharmacologic management of cancer pain. *Oncology* 2004; 18: 1499–1515 discussion 1516, 1520–1, 1522, 1524.
8. Luger NM, Mach DB, Sevcik MA, Mantyh PW. Bone cancer pain: from model to mechanism to therapy. *J Pain Symptom Manage* 2005; 29 (5 Suppl): S32–S46.
9. Cherny N, Ripamonti C, Pereira J et al. Strategies to manage the adverse effects of oral morphine. An evidence-based report. *J Clin Oncol* 2001; 19: 2542–2554.
10. Hanks GW, De Conno F, Ripamonti C et al. Morphine and alternative opioids in cancer pain: clinical recommendations. Expert Working group of the Research Network of the European Association for Palliative Care. *Br J Cancer* 2001; 84: 587–593.
11. Portenoy RK, Conn M. Cancer pain syndromes. In Bruera E, Portenoy RK (eds): *Cancer pain: Assessment and Management*. Cambridge: Cambridge University Press 2003; 89–110.
12. Mercadante S, Ferrera P, Villari P. Is there a ceiling effect of transdermal buprenorphine? Preliminary data in cancer patients. *Support Care Cancer* 2007; 15: 441–444.
13. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006; 104: 570–587.
14. Cherny NI. Sedation for the care of patients with advanced cancer. *Nat Clin Pract Oncol* 2006; 3: 492–500.