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Pain management of the cancer patient
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Introduction: Cancer pain is one of the most important symptoms of malignant disease, which has a major impact on the quality of life of cancer patients. Therefore, it needs to be treated appropriately after a careful assessment of the types and causes of pain.

Areas covered: The mainstay of cancer pain management is systemic pharmacotherapy. This is, in principle, still based on the WHO guidelines initially published in 1986. Although these have been validated, they are not evidence-based. The principles are a stepladder approach using non-opioids, weak and then strong opioids. In addition, adjuvants can be added at any step to address specific situations such as bone or neuropathic pain. Patients, even if they are on long-acting opioids, need to be provided with immediate-release opioids for breakthrough pain. In case of inefficacy or severe adverse effects of one opioid, rotation to another opioid is recommended.

Expert opinion: There is a major need for more and better randomized controlled trials in the setting of cancer pain as the lack of evidence is hampering the improvement of current treatment guidelines.

Keywords: cancer pain, co-analgesics, non-opioids, opioids, WHO guidelines

1. Introduction
Cancer is a multifaceted complex condition affecting physical, psychological, social and spiritual aspects of the life of an individual affected by it. Out of all accompanying symptoms, cancer pain has been recognized as one of the most important ones [1]. A multidisciplinary evidence-based approach is recommended for its treatment, including pharmacological treatments, psychosocial and behavioral interventions, physical therapy and exercise, interventional procedures and spiritual support [2-4].

1.1 Prevalence
Nearly 10 million patients are being diagnosed with cancer annually with an ever-increasing incidence [5,6]. Cancer patients present in 20 – 50% of cases with pain as a symptom [7]. The prevalence of cancer pain depends on the localization and type of cancer; cancers of the head and neck show the highest pain prevalence of 70%. The prevalence increases with progression of cancer and may reach 90% in terminal patients [8]. Pain is also common in cancer survivors with a reported prevalence of 26 – 54% [7].

1.2 Undertreatment of cancer pain
Despite a plethora of guidelines and recommendations, cancer pain still is often undertreated [9]. According to systemic reviews of the literature, nearly half of the patients in pain do not receive adequate treatment [10]. Morphine consumption data and the pain management index are two indicators, derived from World Health Organization (WHO) guidelines, that have been utilized to assess the efficacy of cancer pain treatment; recent studies using these methodologies continue to find undertreatment of cancer pain in multiple settings [9].
It is important to identify the reasons for this situation so that deficiencies can be addressed, ultimately leading to improved quality of care and thereby quality of life of cancer patients. Patients’ beliefs such as fear of addiction and of possible side effects of analgesics, misconceptions of pain meaning disease progression, beliefs that treatment of disease is more important than that of pain are some of the contributing factors for not seeking adequate pain treatment [11]. Healthcare providers such as medical practitioners and nurses play a key role in the delivery of pain management. Here physicians’ lack of knowledge about cancer pain management, inadequate pain assessment and inadequate opioid prescription as well as again fear of causing addiction need to be addressed to achieve better quality of care [12]. System and institutional factors include inadequate referral to appropriate specialties, unavailability of or limited access to certain analgesics, in particular opioids, and inadequate allocation of funds to palliative care [12].

1.3 Characteristics of cancer pain

The causes of pain in cancer patients can be classified as:

1) directly related to cancer, for example, direct invasion or compression of structures by the cancer;
2) related to cancer therapy, for example, due to surgery, chemotherapy or radiotherapy;
3) related to effects of cancer, such as bed sores or debility;
4) other, often age-related, comorbidities such as chronic back pain or osteoarthritis in patients with cancer.

With current advanced cancer therapy, patients’ survival has increased, and as a result, previous cancer patients present increasingly with such issues.

From a therapeutic approach, it is important to classify pain as either nociceptive or neuropathic. Nociceptive pain is defined as ‘pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors’. It is important to consider this when assessing pain, as it will influence treatment strategies. A number of rather specific individual pain syndromes have been described and these may need to be recognized [20].

Breakthrough pain is acute exacerbation of pain of short duration on the background of stable pain, commonly controlled with opioids [21]. A comprehensive assessment of breakthrough pain, encompassing the etiology, intensity, mechanisms and impact on patients’ daily activities should be performed [21]. Assessment tools for the assessment of breakthrough pain are under development; the Breakthrough Assessment Tool is currently at initial validation stage and may become a useful tool in pain assessment [22].

For cognitively impaired patients, assessment tools such as the Abbey pain scale can be applied [23]; furthermore, observation of behavioral patterns is useful [18].

2. Guidelines for treating cancer pain

The original guidelines, published by the WHO in 1986 [24] and updated in 1996 [25], have governed and improved cancer pain relief worldwide and remain an important tool to

- Cancer pain is the most important symptom of malignant disease.
- Cancer pain is commonly undertreated.
- The treatment of cancer pain should follow validated established guidelines.
- Beside opioid analgesics as the mainstay, non-opioids and co-analgesics play an important role in the pharmacological management of cancer pain.
- Despite all progress, the evidence base for cancer pain management remains limited and future better studies addressing multiple areas of uncertainty are required.

This box summarizes key points contained in the article.
improve the current situation, in particular in the developing world. Although these guidelines are not evidence-based, their value in clinical practice is well validated [26,27]. According to these guidelines, overall cancer pain management is based on pharmacological methods as the mainstay and non-pharmacological methods. Pharmacological management is based on the 3-step analgesic ladder. Step 1 recommends use of non-opioids for mild pain, step 2 recommends introduction of weak opioids for moderate pain, and in step 3, strong opioids are introduced for severe pain [18,28]. Among other issues addressed later in the review, one drawback to the WHO stepladder approach is that drug choices are based on severity of pain only, but does not provide guidance to dosing strategies and temporal variations of pain.

The non-pharmacological methods such as physical, psychological and complementary therapies are outside the scope of this paper [18]. Apart from pharmacotherapy, causal treatment options such as chemotherapy, radiotherapy, immune therapy or surgical interventions should be considered as components of the pain management strategy; this may require referral and involvement of appropriate other specialties [29].

Multiple organizations have recently published guidelines for the management of cancer pain [30]; the European Society of Medical Oncology most recently updated its guidelines [10]. In addition to analgesics recommended by WHO analgesic ladder, these guidelines highlight the role of adjuvant analgesics, pharmacological management of opioid-related side effects and use of other non-pharmacological methods. Guidelines like these should govern contemporary cancer pain management. Assessment of outcome should not only focus on the provision of pain relief alone; a simple guidance to outcome assessment should look at the so-called four As (analgesia, activity, adverse effects and addiction), commonly used in non-cancer pain settings.

2.1 Pharmacotherapy for mild cancer pain (WHO step 1)
For the treatment of mild cancer pain, non-opioids such as aspirin, acetaminophen (paracetamol) and NSAIDs are used. NSAIDs, in particular, are recommended as first-line therapy for bone pain [31].

2.1.1 Acetaminophen
Acetaminophen has antipyretic and analgesic properties. There is currently increasing discussion on the limited efficacy of paracetamol and the possibly underestimated adverse effects [32]. In a systematic review, insufficient evidence was found to support the use of acetaminophen in combination with strong opioids [33]. Of particular concern are increasing reports of hepatic toxicity with paracetamol, particularly at doses more than 4 g/day. Most of these overdoses are unintentional and related to multiple analgesics containing acetaminophen and to acetaminophen/opioid combinations and have resulted in FDA advice on dose restrictions [34]. Certain anticancer drugs and paracetamol may interact to cause increased hepatotoxicity [1].

2.1.2 NSAIDs
NSAIDs inhibit cytokines and chemokines, which are mediators of inflammation, in addition to their inhibitory effects on biosynthesis of prostaglandins [35]. This group of drugs exerts analgesic effects on the central and peripheral nervous system; details are still under evaluation [1]. COX, the enzyme blocked by NSAIDs, has two isoenzymes labeled COX-1 and COX-2. COX-1 is primarily a constitutive enzyme, responsible for synthesis of protective prostaglandins that maintain integrity of gastric mucosa and platelet function as well as partially perfusion of compromised kidney. COX-2 is primarily inducible and mediates pain and inflammation, but is also protective in the kidney [28]. The analgesic properties of NSAIDs are dosedependent and have a ceiling effect; however, with increasing dosage, there is an increase in the incidence of side effects without a ceiling effect [36]. There is no evidence for one NSAID being superior to another, but rotation may be useful in case of poor efficacy; non-selective NSAIDs have similar efficacy to COX-2 selective ones [37]. It is useful to combine NSAIDs with acetaminophen, as the efficacy of the combination is superior to each drug used on its own [38]. There is weak support from a systematic review that NSAIDs added to strong opioids in cancer pain improve analgesia or reduce opioid requirements [33].

The classical non-selective NSAIDs such as naproxen and ibuprofen can cause gastric and intestinal ulceration, renal impairment and platelet inhibition. Substitution with a selective COX-2 inhibitor such as celecoxib or etoricoxib reduces the gastrointestinal (GI) toxicity significantly and causes no platelet inhibition; there may even be a reduced risk of acute kidney injury with COX-2 selective agents [39]. The assumed increased risk for cardiovascular complications such as myocardial infarction and stroke with COX-2 inhibitors [1] could not be confirmed [40]; thromboembolic adverse effects are a class effect of all NSAIDs, and some COX-2 inhibitors such as celecoxib are actually safer than some non-selective NSAIDs such as diclofenac [41].

Even in the elderly, NSAIDs could be an effective treatment option in spite of concerns about their safety profile as long as contraindications are considered; they should be prescribed at the lowest effective dosage for the shortest possible duration [42].

2.2 Pharmacotherapy for moderate cancer pain (WHO step 2)
For the management of moderate cancer pain, the clinical relevance of the recommendations of WHO analgesic ladder step 2 to use so-called weak opioids is increasingly being debated [43,44]. Although the guidelines recommend weak opioids such as codeine, dihydrocodeine (DHC) and tramadol administered orally in combination with non-opioids for the management of moderate pain, there is increasing support for the omission of this step and direct progression to low-dose strong opioids [10]. However, there is ongoing debate
on this issue [45]; in many countries, weak opioids are an important option to treat cancer pain in view of poor access to strong opioids as outlined above.

2.2.1 Tramadol
Tramadol is a centrally acting atypical analgesic, which inhibits re-uptake of serotonin and more importantly noradrenaline. It is metabolized into O-desmethyl tramadol (M1), which has µ-opioid receptor agonist activity [46,47]. Tramadol is usually administered orally, but can be given parenterally or rectally, if required. Its low abuse potential, worldwide availability, reduced opioid-related adverse events (e.g., constipation) and specific activity in neuropathic pain make it the most useful of the weak opioids [18,48]. However, there is a concern that tramadol can precipitate serotonin syndrome either with significant overdose or when co-administered with other serotonergic drugs.

2.2.2 Codeine
Codeine is an inactive prodrug of morphine; its analgesic efficacy relies on liver metabolism by the CYP2D6 enzyme, leading to its active metabolite morphine. Polymorphisms in CYP2D6 result in a range of metabolic patterns from ultrarapid to ultra-slow metabolizers, who experience anything from significant morphine effects (and adverse effects) to no analgesia at all [1,49]. Further disadvantages are variable oral bioavailability and a high propensity to induce constipation; overall codeine is not a useful choice in the setting of cancer pain, as long as other opioids are available [18].

2.2.3 Dihydrocodeine
DHC is a semisynthetic analog of codeine, with an equivalent potency of 1:3 ratio of subcutaneous DHC to morphine. As it does not require metabolic conversion [49], it is a more reliable step 2 weak opioid than codeine, but advantages over low doses of strong opioids have never been shown.

2.3 Pharmacotherapy for severe cancer pain
(WHO step 3)
Severe cancer pain is commonly treated with strong opioids, if feasible by oral administration. Opioids are classified as full agonists, partial agonists, agonist–antagonists or antagonists according to their interaction with opioid receptors. Opioids with full agonist properties do not show ceiling effect for analgesia and dose increase is limited by side effects. Opioids with either agonist–antagonist or partial agonist properties have ceiling effect for analgesia; therefore, they may not be ideal for cancer pain management [28]. There is no evidence of one opioid agonist being superior to another with regard to efficacy [1].

2.3.1 Strong opioids used in cancer pain treatment
2.3.1.1 Morphine
Morphine is a pure opioid agonist available as oral immediate (IR) or controlled release (CR) preparations (12 or 24 h duration of effect) and for subcutaneous, intramuscular and intravenous (i.v.) administration as well as rectal administration in most countries. The half-life of IR preparations is 2 – 3 h with 20 – 30% bioavailability following oral administration. The oral to parenteral conversion is about 3:1 [50]. Morphine is metabolized in the liver into morphine-6-glucuronide (M6G), an active metabolite having analgesic properties exceeding those of morphine itself and morphine-3-glucuronide (M3G), devoid of analgesia. M6G accumulation in renal failure can cause increased adverse effects and potentially respiratory depression. The neurotoxic and hyperalgesic effects of M3G may be responsible for reduced efficacy and increased adverse effects with escalating dosages of morphine. Genetic variability in morphone metabolism may play a role in the manifestation of these effects [28,50], but the effects are also influenced, as are those of all other opioids, by genetic variants of the OPRM1 gene, encoding the µ-opioid receptor [51].

2.3.1.2 Oxycodone
Oxycodone is a synthetic opioid with comparatively high K-receptor affinity; the clinical relevance of this effect is debated. A brain:plasma ratio of 3:1 of unbound drug explains why oxycodone has relative less affinity for µ receptors than morphine, but a higher potency [52]. It is available in oral IR and CR formulations as well as for parenteral use. Oxycodone has a bioavailability of 60 – 87% following oral administration. The half-life of IR oxycodone is about 2 – 3 h. Although oxycodone is metabolized in liver into noroxycodone and oxymorphone, analgesia is mainly attributable to the parent drug. The side effect profile of this drug is similar to morphine, although it causes less nausea, vomiting, pruritus and hallucinations [1,18,49]. Constipation is one of the known adverse effects of opioids and often refractory to conventional treatment in cancer patients. Combination preparations of slow-release naloxone and slow-release oxycodone provide analgesia and reduce constipation at the same time. When administered orally, naloxone acts primarily on GI opioid receptors reducing the constipating effect of oxycodone. However, due to an extremely high first-pass effect, it has very low oral bioavailability and does not antagonize the analgesic effect of oxycodone in the CNS. Two recent studies, one in cancer patients and the other in non-cancer chronic pain patients, show that this combination was well tolerated by both groups, with significantly less GI complications and similar analgesic profile to oxycodone [53,54]. There is a recommended daily maximum dose of 80 mg to avoid systemic naloxone effects. In severe hepatic failure, naloxone may no longer undergo significant first pass metabolism and may consequently antagonize central opioid receptors, impairing the analgesic effect of oxycodone [6].

2.3.1.3 Hydromorphone
Hydromorphone is a semisynthetic opioid with mainly µ-agonist activity. It is 5 – 10 times more potent compared
to morphine and therefore particularly useful, when administration of smaller volumes is preferred, as in subcutaneous infusion. The half-life is about 2.5 h. CR preparations are available [55]. Hydromorphone is metabolized in the liver mainly to hydromorphone-3-glucuronide (H3G) and small amount of 6-hydroxy-hydromorphone. H3G may cause neurotoxic side effects, particularly when retained in patients with impaired renal function and following prolonged use [49].

2.3.1.4 Fentanyl
Fentanyl is a lipophilic μ-receptor agonist, 100 times more potent than morphine. Due to extensive first-pass metabolism, oral administration is ineffective. However, different formulations for other routes of administration are available: parenteral as well as transdermal and transmucosal such as intranasal and sublingual [56]. There may be a reduced side-effect profile compared to morphine (nausea, vomiting, constipation, sedation and pruritus), in particular with transdermal use [57]. Fentanyl is metabolized by CYP3A4 into inactive metabolites; thus it is a safe option in patients with renal impairment [58]. For breakthrough pain, IR preparation with rapid response, such as oral transmucosal fentanyl or intranasal fentanyl spray, is available [59]. Intranasal fentanyl is particularly useful due to its rapid uptake, even in patients with dry mouth [21].

2.3.1.5 Methadone
Methadone is a μ- and δ-opioid receptor agonist, but also an NMDA receptor antagonist and a noradrenaline and serotonin reuptake inhibitor [60]. These properties might explain the benefits some patients achieve when rotated from other opioids to methadone and possibly its efficacy in neuropathic pain. The pharmacokinetics are complicated by large interindividual variability of the plasma half-life and is 15 – 60 h; it takes about 2 – 5 days before steady-state plasma levels are reached. Due to this, dose escalation should be done carefully [60]. In high doses, it may provoke cardiac dysrhythmias due to QT prolongation [61]. Compared to morphine, it causes less nausea, vomiting and constipation. Methadone is metabolized in the liver and GI tract into inactive metabolites. Drugs commonly used in cancer patients such selective serotonin reuptake inhibitors (SSRIs), ketoconazole, omeprazole can potentiate methadone by inhibiting cytochrome enzymes (mainly CYP2B6) involved in its metabolism [62]. The inactive metabolites are eliminated via GI tract and kidneys, thus making it safer in patients with renal impairment. Methadone may become an opioid of choice for patients on dialysis [63]. Because of complex pharmacokinetics and equianalgesic conversion variability, prescribing should be done by experts [1,18,49].

2.3.1.6 Buprenorphine
Buprenorphine is an opioid agonist-antagonist that is about 100 times more potent than morphine. Sharing features inherent to this group of drugs, it has potentially a ceiling effect, but only at extremely high doses. Buprenorphine can be given by the sublingual (as low oral bioavailability), transdermal or parenteral route and can substitute high doses of other opioids contradicting previous concerns [64]. Buprenorphine is metabolized in liver to active metabolites and excreted through GI tract, thus making it safe in patients with renal impairment. Compared to other opioids, it has better side effect profile in terms of nausea, vomiting and constipation and a lower risk of respiratory depression [65]. Although there is increasing use of buprenorphine in cancer pain, data are still limited [66], but suggest potential advantages, for example, over transdermal fentanyl [67].

2.3.1.7 Tapentadol
Tapentadol is centrally acting novel synthetic opioid developed for the management of mild-to-moderate pain [68] and has been used successfully in cancer pain [69]. It has less affinity for μ-receptors compared to strong opioids and inhibitory effects on central norepinephrine reuptake. Despite an opioid receptor affinity 20 times less than that of morphine in humans, a recent prospective study has shown a conversion ratio of 1:3:3 between oral morphine and tapentadol bidirectionally [70]. The reduced μ-receptor affinity confers less opioid-related side effects, mainly of GI origin (nausea, vomiting and constipation) than equianalgesic doses of conventional opioids [68]. The monoaminergic effects support the concept of superior efficacy in neuropathic pain [71].

Other opioid agonists such as meperidine (pethidine) and propoxyphene are not recommended for cancer pain management due to neurotoxicity of their metabolites. Partial agonists are not suitable as well due to their inherent ceiling effect for analgesia [1].

2.3.2 Practical management of strong opioids
There is ongoing debate on the method to initiate opioids in cancer pain management, but only limited evidence to support one single approach. Opioid titration using sustained release oxycodone and IR morphine has been supported in pilot studies [72]. Subsequent to the titration phase, dosage is adjusted according to patient’s response. Conventionally, the dose increment is calculated 33 – 50% of average total daily dosage during the preceding few days [73]. Transdermal opioids are recommended as second-line therapy when oral administration is not applicable. In spite of recommendations, the selection of an opioid is governed by factors such as clinicians’ experience, patients’ prior experience, cost and availability of specific opioids [73].

2.3.2.1 Opioid rotation
Opioid rotation or opioid switching describes the process of substituting a strong opioid in step 3 with another strong opioid [74]. The process is aimed to increase either opioid efficacy or reduce adverse events of opioids. The effectiveness of another opioid may be due to the phenomenon of incomplete cross-tolerance or the presence of variable responses at
multiple μ-receptor subtypes [75]. For dose calculation of equivalency, conversion tables are being used; however, these are based on data derived from studies on acute pain settings [76]. Such tables need to be used with caution due to the interindividual variability of response to opioids; to minimize the risk of overdose, dose reduction and clinical judgment is important. A careful approach taking into consideration other confounding factors such as associated medical and psychological factors has been proposed [77].

3. Management of breakthrough pain

Breakthrough pain is defined as episodic bursts of pain of short duration on the background of stable pain controlled by opioids. Guidelines recommend comprehensive assessment followed by individualized plan for the pain management [45,78]. IR opioid preparations are recommended as the first-line therapy for breakthrough pain. Advantages of IR opioid preparation are ease of administration, relatively fast onset of analgesia and quite extensive experience in their use. Morphine, oxycodone, hydromorphone, buprenorphine and methadone are available as IR preparations [21]. The other options are intranasal or transmucosal fentanyl [56,59] and i.v. morphine. Studies have demonstrated the efficacy of intranasal fentanyl over transmucosal preparation [45]. Intranasal fentanyl has a high bioavailability (70 - 90%) and peak plasma levels are reached in about 13 min following administration [21]. Two recent meta-analyses showed that transmucosal fentanyl preparations are more efficacious than oral morphine in this setting [79,80].

Additionally non-opioid pharmacotherapy such as acetaminophen, NSAIDs, bisphosphonates, clonidine and ketamine lozenges may be useful. In addition, guidelines recommend application of non-pharmacological methods such as radiotherapy, surgical interventions and regional techniques [78].

4. Use of co-analgesics and adjuvants

These are medications not commonly regarded as analgesics but can be used to enhance the effect of primary analgesics or in certain selected situations as primary analgesics. Co-analgesics are used, in particular, in specific diagnoses or clinical scenarios such as neuropathic pain, bone pain or visceral pain. These drugs can be incorporated into each step of the analgesic ladder depending on the clinical situation to achieve optimum pain relief and relief from symptoms. Adjuvants may have other indications apart from achieving analgesia, which should be taken into consideration during prescription.

4.1 Antidepressants

Antidepressants play an important role in the management of neuropathic pain conditions. Tricyclic antidepressants (TCAs) such as amitriptyline or nortriptyline and selective serotonin–norepinephrine reuptake inhibitors (SNRIs) such as duloxetine or venlafaxine are commonly in use. SSRIs such as fluoxetine have limited application in neuropathic pain due to low efficacy [81].

4.2 Tricyclic antidepressants

TCAs are generally considered first-line therapy in neuropathic pain, also in cancer patients. They are very effective in a number of different neuropathic pain settings such as pain arising from nerve compression and infiltration and post-chemo- and radiotherapy [81]. The numbers-needed-to-treat (NNTs) for TCAs in neuropathic pain are in the range of 2.1 – 2.8 [13]. As a group, they inhibit reuptake of norepinephrine and serotonin thereby enhancing descending inhibitory pathways of pain with additional effects on NMDA receptors and sodium channels [81]. The antidepressant effects may be additionally beneficial, particularly in cancer patients, who are more prone to depression; furthermore amitriptyline enhances the antihyperalgesic effects of co-administered morphine [82]. The analgesic dose required is less than the antidepressant dose. TCAs have anticholinergic properties causing dry mouth, blurred vision and in high doses can cause cardiac dysrhythmias, conduction abnormalities, narrow-angle glaucoma and prostatic hyperplasia. As a result, TCAs are often not suitable for elderly patients and poorly tolerated [1,13,28]; they should be started at low doses at night to improve compliance. Abrupt discontinuation of higher doses of TCAs may cause withdrawal symptoms [81].

4.3 Serotonin–norepinephrine reuptake inhibitors

SNRIs are showing promising results in the treatment of cancer-related neuropathic pain [31,81]. Compared to TCAs, these have a better side-effect profile. Both venlafaxine and duloxetine have also been found to be effective for hot flushes in patients on hormonal therapy for breast cancer. Duloxetine interacts with concomitantly administered tamoxifen, reducing the efficacy of the anticancer medication [1].

4.4 Anticonvulsants

Anticonvulsants are another group of medications that have become established as first-line treatment of neuropathic pain. The evidence is limited for older anticonvulsants such as carbamazepine, phenobarbital and phenytoin with the exception of carbamazepine in trigeminal neuralgia. These are also hepatic P450 enzyme inducers and interact thereby with certain anticancer therapies and steroids, which are metabolized by the same system. In general, anticonvulsants are used for neuropathic pain at the same dosage as for management of seizures [28].

4.5 Gabapentin and pregabalin

Gabapentin and pregabalin are the two anticonvulsants with the best evidence base for the treatment of neuropathic pain. Both act as modulators of the α2δ subunit of voltage-gated calcium channels presynaptically, thereby inhibiting excitatory neurotransmitter release. For both drugs, NNTs for
neuropathic pain range from 4.2 to 6.4 [13]. Gabapentin given orally has low bioavailability and shows non-linear pharmacokinetics with increasing dose due to saturation of the transport mechanism. Pregabalin is more potent, better absorbed and has a linear pharmacokinetic profile [31,81]. Both these drugs are primarily excreted unmetabolized through the kidney and have minimal drug interactions. Dosages have to be reduced in renal failure. Common side effects are somnolence, dizziness, peripheral edema and weight. Both drugs are also effective in chemotherapy- or radiotherapy-induced mucositis and have significant anxiolytic properties [13,28,31].

4.6 Topical agents
Topical agents for the treatment of neuropathic pain include lidocaine and capsaicin [13]. Lidocaine 5% patches were developed for post-herpetic neuralgia, but are also effective in other localized neuropathies, in particular those accompanied by allodynia [13,31]. The major advantage is the lack of systemic side effects; local skin irritation following application may be the only relevant complication. Capsaicin, acting on the vanilloid receptor TRPV1 was again found to be effective for post-herpetic neuralgia, when applied as a high-concentration patch (8%) [81].

4.7 Corticosteroids
Corticosteroids are widely used as co-analgesics in cancer patients [81]. They are indicated to alleviate pain in spinal cord compression, superior vena cava syndrome, raised intracranial pressure headache, metastatic bone pain, hepatic capsular distension and neuropathic pain. Relieved pressure due to anti-inflammatory effects is the most likely mechanism of action. Apart from analgesia, corticosteroids have been used in cancer patients to improve appetite and mood and as an antiemetic. Dexamethasone has been preferred due to its reduced mineralocorticoid activity, long duration of action and potency [81]. With prolonged use, patients have to be monitored for the well-known complications such hyperglycemia, peptic ulcers, cushingoid habitus and neurological complications [1,83].

4.8 Ketamine
Ketamine as an NMDA receptor antagonist is widely used in cancer pain. Ketamine can be administered parenterally (i.v. or subcutaneously), but there are also increasing reports on oral, intranasal and transmucosal administration [84]. There is contradictory data on its efficacy; a recent randomized controlled trial (RCT) may have failed due to inappropriate patient selection [85]. Use in increasing doses may be limited by psychomimetic adverse effects and potential other toxicity.

4.9 Cannabinoid
Cannabinoid use for therapeutic purposes in neuropathic pain remains controversial with contradictory results on efficacy and potential abuse [50]. However, there are some positive results in neuropathic pain caused by cancer and a nasal spray is licensed in some countries [13]. Other benefits are a potent anti-emetic effect and improvement of appetite.

4.10 Bisphosphonates
Bisphosphonates are beneficial in cancer-related bone pain, in particular prostate and breast cancer [81]. They inhibit osteoclastic activity and hence bone resorption, but further research is needed to identify the most useful compound and treatment schedule [86-88].

4.11 Denosumab
Denosumab, a human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANKL), has been shown to reduce bone loss [18]. Positive outcome has been seen in early studies on patients with bone metastases, who have been treated with denosumab. Compared to bisphosphonates, denosumab has better analgesic profile, prevents skeletal-related events and less adverse effects [89].

5. Conclusions
Cancer pain remains one of the most important and most distressing symptoms of malignancy. The management of this symptom requires proper assessment of the patient and should establish a pain diagnosis. Often pain occurs in multiple locations and can have multiple causes and mechanisms. Treatment of cancer pain relies primarily on systemic pharmacotherapy and is based on guidelines, initially developed by the WHO and then fine-tuned in recent years. Although there is increasing evidence in certain areas of cancer pain management, overall treatment is still based on recommendations that rely primarily on weak data and expert opinion. However, this approach has resulted in successful treatment in many patients. Future developments should focus on a better evidence base for the guidelines, but also on better access to medications and appropriate therapies in the developing world.

6. Expert opinion
The key problem with the whole issue of cancer pain management is the lack of definitive evidence in many areas. This is most obvious with regard to the WHO guidelines, which were developed on the basis of expert opinion. Although they have been validated and proven to be effective in a large number of patients, there is a significant lack of scientific evidence supporting many of the concepts including the stepladder approach. For example, the European Palliative Care Research Collaborative attempted to support the concept of combining opioids, a common clinical practice, by a meta-analysis [90]. However, the authors were only able to identify two studies on relatively low evidence levels, which resulted in a weak recommendation with caveats. The reason is the lack of any RCT examining the issue of combining opioids.
Similar issues can be found in many other key areas of cancer pain management [91]. The notion, that morphine is the first-line opioid for cancer pain treatment, repeated in guideline after guideline, might need to be revised, but good data are lacking. Similarly, possibly even more disappointing, dosing recommendations for treatment of breakthrough pain have not been established in RCTs. Again, all recommendations in guidelines are primarily based on expert opinion [91].

This list can be continued; the role of COX-2 inhibitors and the choice of co-analgesics in neuropathic pain states have not been established on the basis of RCTs in cancer pain, but only based on results in patients with benign conditions. Even the optimal treatment of bone pain is currently not based on proper scientific evidence and any recommendations on choice of compound, doses and treatment intervals are again primarily based on expert opinion.

Another example is the concept that non-opioids should be continued when opioids are started is supported primarily by literature from acute post-operative pain management, where the concept of multimodal analgesia is well established and supported by RCT and meta-analyses. However, the setting of chronic cancer pain is very different in many aspects. Here the data are very limited and evidence-based guidelines can only make weak recommendations on the usefulness of non-opioids in the cancer pain setting [45].

One of the completely unresolved issues in cancer pain treatment is the role and relevance of the step 2 of the WHO ladder, that is, the use of so-called weak opioids. Already the term ‘weak opioids’ is poorly defined, the separation from strong opioids arbitrary and a specific pharmacodynamic differentiation does not exist. Furthermore, advantages of one weak opioid over another have not been properly evaluated; the question of ceiling effects has also not been addressed. Last but not the least, there remains the key question if step 2 is actually a really useful step or if it should not be omitted in favor of low doses of strong opioids [45]. This has led some authors to question if the step 2 is only a ‘didactic instrument’ [43] or an ‘educational substitute for morphine’ [92]. In 2014, we are not closer to an answer to these questions; this was recently again expressed in an European Association for Palliative Care guideline publication that stated ‘The utility of step II opioids in the WHO method has been addressed in three trials, all of which have significant methodological flaws, insufficient statistical power, and selection bias.’ [45].

Overall, shortage of RCTs remains the key concern here. This is to a large extent a result of the difficulties of performing RCTs in a cancer pain population. The reasons for this are obvious and include difficulties in standardizing treatments over often heterogeneous patient populations, ethical issues of enrolling cancer pain patients in yet another clinical trial, the difficulties of identifying appropriate comparators and the multiple other symptoms in cancer patients.

Nevertheless, continuing attempts need to be made to design and perform proper RCTs answering key questions in cancer pain management to permit better evidence-based guideline development in the future.

### Declaration of interest

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### Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


** An excellent review of the concepts underlying cancer pain management.


** Up-to-date evidence-based guidelines for cancer pain management – the ‘must read’ reference.


• An excellent review of current concepts and tools for cancer assessment.
• The first validation study of the World Health Organization (WHO) guidelines—of historic value.
• The largest validation study of the WHO guidelines.
• An interesting comparative paper of current cancer pain guidelines.
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• A summary of practical recommendations on selection and use of opioids in cancer pain management.
• Excellent meta-analysis of the risks related to the use of non-selective and COX-2 selective NSAIDs.
• A summary of practical recommendations on selection and use of opioids in cancer pain management.
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78. An useful resource on breakthrough pain management.


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