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REVIEW ARTICLE

Nonopioid Drugs in the Treatment of Cancer Pain

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ABSTRACT

The WHO analgesic ladder for the treatment of cancer pain provides a three-step sequential approach for analgesic administration based on pain severity that has global applicability. Nonopioids were recommended for mild pain, with the addition of mild opioids for moderate pain and strong opioids for severe pain. Here, we review the evidence for the use of nonopioid analgesic agents in patients with cancer and describe the mode of action of the main drug classes. Evidence supports the use of anti-inflammatory drugs such as acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) for mild cancer pain. Adding an NSAID to an opioid for stronger cancer pain is efficacious, but the risk of long-term adverse effects has not been quantified. There is limited evidence to support using acetaminophen with stronger opioids. Corticosteroids have a specific role in spinal cord compression and brain metastases, where improved analgesia is a secondary benefit. There is limited evidence for adding corticosteroids to stronger opioids when pain control is the primary objective. Systematic reviews suggest a role for antidepressant and anticonvulsant medications for neuropathic pain, but there are methodologic issues with the available studies. Bisphosphonates improve pain in patients with bony metastases in some tumor types. Denosumab may delay worsening of pain compared with bisphosphonates. Larger studies of longer duration are required to address outstanding questions concerning the use of nonopioid analgesia for stronger cancer pain.

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INTRODUCTION

Up to 90% of patients with cancer experience pain at some stage of their cancer journey, with a third rating the intensity of their pain as moderate to severe,[1-3] and up to half being undertreated.[1,4,5] The WHO analgesic ladder, which provides guidelines for the treatment of cancer pain, was published in 1986 and updated in 1996.[6] The guidelines recommend a sequential three-step approach for analgesic administration based on pain severity, with nonopioids for mild pain, weak opioids for moderate pain, and strong opioids for severe pain. In addition to drug selection based on the severity of the pain and individualized for the patient, recommendations include the use of oral medications whenever possible, with fixed scheduled dosing according to the pharmacokinetics of the drug rather than on demand and regular assessment and re-evaluation of the pain. It is recommended that the drugs used in step 1 be continued as opioids are added. The rationale for adding a nonopioid to an opioid is to add a drug with a different mechanism of action with the aim of improving analgesic control and/or reducing opioid requirements and minimizing opioid adverse effects.[7]

When the WHO guidelines were developed to address the issue of undertreated pain, there was limited evidence to inform them. Rather, they were developed to provide a framework to guide international policy for the treatment of cancer pain with pain relief that was affordable and readily accessible globally. Despite controversies about whether the second step should be omitted and whether nonopioid analgesic agents should be continued once an opioid is required, the WHO analgesic ladder remains the mainstay of management of cancer pain.[8] Individual studies and systematic reviews that have evaluated the WHO guidelines have shown that they can control cancer pain in 45% to 100% of patients.[9-11]

The most common nonopioid agents used to treat cancer pain include acetaminophen/paracetamol; anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids; antineuropathic agents, which include tricyclic antidepressants and anticonvulsants; and bisphosphonates. The mode of action of each drug is outlined in Table 1, and the major studies that have evaluated their use in people with cancer are outlined in Tables 2 to 6.

ACETAMINOPHEN/PARACETAMOL

Acetaminophen (known in some countries as paracetamol) is an inexpensive analgesic that is used globally. Although it was developed over a hundred years

Table 1. Pharmacology of Major Classes of Nonopioid Analgesics

Class of Drug	Pharmacokinetics	Analgesic Mode of Action	Common Toxicities	Medication Interactions	Major Precautions
Acetaminophen	Rapid and complete absorption from GI tract Hepatic conjugation with glucuronide and sulphate metabolites Peak plasma concentration in 30-60 minutes Half-life approximately 2 hours	Exact mechanism remains unclear; inhibits production of lipooxygenase and cyclooxygenase → decrease prostaglandin and interleukin-1 in hypothalamus; release of endogenous opioids that inhibit descending pain pathways[12] Preclinical models suggest role for endocannabinoid system[14]	In overdose: hepatotoxicity, acute renal tubular necrosis Rare: idiosyncratic fatal hepatotoxicity	Potential to increase international normalized ratio in patients on warfarin[13] Risk of increased metabolism with anticonvulsants, carbamazepine, barbiturates Potential interaction with tyrosine kinase inhibitors (sorafenib, dasatinib, imatinib), leading to inhibition of acetaminophen glucuronidation[15]	Use with care in patients with hepatotoxicity
NSAIDs	Complete bioavailability; binds to albumin; minimal first-pass hepatic metabolism Half-life approximately 2-2.5 hours Marked individual variation	Inhibit cyclooxygenase → decrease conversion of arachidonic acid to prostaglandin, thromboxane, and prostacyclin synthesis Possibly also non–prostaglandin-mediated mechanisms	Dyspepsia, GI bleeding, cardiovascular, nephrotoxicity, hypertension, transaminitis[14,16]	Risk of drug interactions with antiplatelet and anticoagulant agents, antihypertensives, corticosteroids	Recent peptic ulcer disease, prior NSAID gastroduodenopathy, bleeding diathesis, renal disease, major cardiovascular disease
Corticosteroids	Dexamethasone: After parenteral administration, plasma levels peak within 5 minutes Minimally protein bound Hepatic metabolism is slow, and excretion is mainly in the urine Half-life approximately 3-5 hours Prednisolone and prednisone: Highly protein bound Peak concentration 1-2 hours after oral dose Rapid conversion from prednisone into prednisolone in the liver	Exact mechanism remains unclear, but potential effects at all steps of nociception (transduction, transmission, modulation, and pain perception)[17] Mediate their anti-inflammatory effect by inhibition of collagenase and proinflammatory cytokines or stimulating lipocortin production[18] Reduce vascular permeability[17] Inhibit prostaglandin synthesis[17]	Immunosuppression Sodium and water retention, hypertension Increased appetite, emotional lability, depression, insomnia, psychosis Hyperglycemia Myopathy Cushingoid appearance Impaired wound healing, skin thinning, osteoporosis, avascular necrosis of femoral head Cataracts Dyspepsia, peptic ulceration, fatty liver Adrenal insufficiency on abrupt cessation after longer duration use[17,19]	NSAIDs Anticoagulants	Concurrent NSAID use Diabetes Active peptic ulcer disease
Tricyclic antidepressants, eg, amitriptyline, imipramine (tertiary amines), nortriptyline (secondary amine)	Genetic polymorphisms in metabolic pathways result in large pharmacokinetic variability	Inhibit presynaptic update of serotonin and noradrenalin enhancing pain inhibitory pathways; block voltage-dependent sodium channels[20]	Antimuscarinic side effects (eg, dry mouth, constipation, urinary retention, blurred vision) Postural hypotension Gait disturbance Sedation Confusion Sudden cardiac death[22]	Anticholinergics Psychoactive medications Class IC antiarrhythmics and selective serotonin reuptake inhibitors metabolized by P4502D6 can lead to toxic concentrations of tricyclic antidepressants[22]	Cardiac conduction blocks Arrhythmia epilepsy[21]

(continued on following page)

Table 1. Pharmacology of Major Classes of Nonopioid Analgesics (continued)

Class of Drug	Pharmacokinetics	Analgesic Mode of Action	Common Toxicities	Medication Interactions	Major Precautions
Gabapentin, pregabalin	Gabapentin circulates mainly unbound; renal excretion unchanged: dose may need reduction in renal impairment Pregabalin is rapidly absorbed after oral administration, with 90% oral bioavailability independent of dose; renal excretion unchanged: dose may need reduction in renal impairment	Block $\alpha_2\delta$ subunit of voltage-dependent calcium channels[21]	Somnolence Dizziness Peripheral edema Nausea Ataxia Vertigo Asthenia Dry mouth	Psychoactive medications may potentiate side effects	Suicidal ideation
Carbamazepine	Slow oral absorption Peak concentration 4-24 hours Steady-state depends on autoinduction by carbamazepine and heteroinduction by other enzyme-inducing medication and ranges between 1 and 2 weeks Conjugated metabolites excreted in the urine	Blocks voltage-dependent sodium channels[20]	Dermatologic reactions Hypersensitivity Seizures Renal and hepatic dysfunction Aplastic anemia and agranulocytosis Anticholinergic effects Suicidal ideation Confusion	Interactions between CYP3A4 inducers or inhibitors and carbamazepine Monoamine oxidase inhibitors	Bone marrow depression Systemic lupus erythematosus Hepatic porphyria Hepatic failure Atrioventricular block
Bisphosphonates	Poor oral absorption Renal excretion (approximately 70%), remainder taken up by bone Half-life elimination 21-35 hours	Inhibit osteoclast bone resorption by attaching to hydroxyapatite binding sites; decrease osteoclast activity by decreasing osteoclast progenitor cells and increasing osteoclast apoptosis	Acute-phase reactions Ocular inflammation Renal toxicity Electrolyte disturbance Hypocalcemia Osteonecrosis of jaw	Aminoglycosides and phosphate supplements may increase risk of hypocalcemia NSAIDs increase risk of gastric ulceration	Creatinine clearance $<$ 30 mL/min
Denosumab	Administered subcutaneously Not renally excreted Half-life elimination approximately 28 days	Fully human monoclonal antibody that binds RANKL, which regulates migration of tumor cells into bone; inhibits RANKL-mediated osteoclastogenesis → less bone resorption[23]	Acute-phase reactions Fatigue Headache Nausea Skin rash Hypocalcemia Osteonecrosis of jaw	May interact with immunosuppressive drugs, leading to higher risk of infection	Hypocalcaemia
Lignocaine	Parenteral class Ib local anesthetic agent Lignocaine is 90% metabolized by cytokine P450, and metabolites are all renally excreted Half-life 1.5-2 hours	Blocks voltage-gated sodium channels	Restlessness, tremor, convulsions Drowsiness Respiratory failure Dysphoria Euphoria Muscle twitching Ventricular tachycardia and fibrillation	Cimetidine β-Blockers Phenytoin	Cardiac failure Heart block Arrhythmia Hypokalemia Hypertension Hepatic failure Renal failure
Ketamine	Dissociative anesthetic agent Rapid absorption and wide distribution, including in the brain 20%–50% bound to plasma proteins; extensive hepatic metabolism, with one active metabolite (norketamine)	Interacts with *N*-methyl-D-aspartate receptors, interrupts cholinergic transmission, and inhibits noradrenalin and 5-hydroxytryptamine uptake[24]	Hypertension and tachycardia Emergent phenomena and psychomimetic effects (hallucinations, disconnection, disassociation, vivid dreams), sedation, drowsiness Raised intracranial and intraocular pressure Delirium Impaired bladder function[24]	Psychoactive medications (potentiate neurologic toxicity) Medications with hypertensive effect	Raised intracranial or intraocular pressure Conditions where significant hypertension would be hazardous (eg, cerebrovascular disease) Psychiatric illness Delirium Uncontrolled seizures[24]

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; RANKL, receptor-activated nuclear factor κB ligand.

ago, its mode of action for pain relief has not been fully elucidated. It is sometimes classified as an NSAID, but its mechanism of action is not the same.[25] Acetaminophen is well tolerated with a good safety profile at therapeutic doses. In overdose, hepatotoxicity and acute renal tubular necrosis can occur. Patients may be at higher risk of hepatotoxicity after starvation, fasting, or chronic alcohol abuse, but hepatic toxicity is rare in doses less than 8 g daily, even in patients with chronic liver disease.[20,26] Serious hypersensitivity reactions to acetaminophen are extremely rare (Table 2).

Acetaminophen for Acute Pain

Systemic reviews and meta-analyses have shown that acetaminophen is more effective than placebo for acute postoperative pain.[33-35] The optimal dose of acetaminophen remains uncertain. A Cochrane review of 51 studies including 5,762 postoperative participants and using an end point of 50% total pain relief found that a single dose of acetaminophen was significantly more effective than placebo, with a number needed to treat of 3.5 patients (95% CI, 2.7 to 4.8 patients) for 500 mg of acetaminophen, 4.6 patients (95% CI, 3.9 to 5.5 patients) for 600 to 650 mg, and 3.6 patients (95% CI, 3.4 to 4.0 patients) for 975 to 1,000 mg.[33] There was no difference in adverse effects in the acetaminophen arms compared with placebo.[33] Another Cochrane review comprising 20 studies and 2,641 patients evaluated oxycodone with and without acetaminophen for acute postoperative pain; the number needed to treat for oxycodone 15 mg was 4.6 patients (95% CI, 2.9 to 11 patients) compared with 2.7 patients (95% CI, 2.4 to 3.1 patients) for oxycodone 10 mg and acetaminophen 650 mg.[36]

Acetaminophen for Patients With Cancer

There is good evidence that acetaminophen is effective for treating mild cancer pain.[37] There is limited evidence for adding acetaminophen to an opioid, and practice varies globally; patients in Europe and Australasia generally remain on acetaminophen once opioids are required, but in North America, acetaminophen is generally discontinued once strong opioids are initiated. A systematic review evaluating acetaminophen in addition to opioids in five small randomized controlled trials (RCTs) involving 200 patients with cancer found no benefit to adding acetaminophen in four of the five studies.[38] The positive study used a cross-over design.[28] Patients reported a modest improvement in pain and overall well-being while on acetaminophen (1 g every 4 hours five times a day), with a nonsignificant preference for analgesic control during the period they were on acetaminophen.[28] A recent RCT evaluated the efficacy of oxycodone (5 mg)/acetaminophen (325 mg) compared with placebo every 6 hours for 3 days for pain caused by bone metastases in 246 patients already on opioids.[32] Although the oxycodone/acetaminophen group had improved pain relief, less breakthrough pain, and reduced need for rescue pain relief, the study design does not allow the relative contribution of each agent in the combination to be determined.

NSAIDS

NSAIDs are a heterogeneous group of drugs that inhibit cyclooxygenase (COX), leading to a reduction of the conversion of arachidonic acid to thromboxane A_2 and prostaglandin synthesis (Table 1).[39] There are two main forms of COX—COX-1 (including a variant known as COX-3) and COX-2. Although COX-1 is present in most tissues, COX-2 is mainly expressed in inflamed tissue.[39,40] Most NSAIDs are nonselective inhibitors of COX-1 and COX-2, but newer agents such as celecoxib have much greater affinity for the COX-2 isoform.[40] The selective COX-2 inhibitors are substantially more expensive than the older nonselective agents.

Adverse Effects

The toxicity profile for NSAIDs includes GI and cardiovascular effects, hepatotoxicity, and nephrotoxicity, including renal failure caused by renal vasoconstriction, hypertension, and electrolyte disturbances.[16,41] The risk of toxicity is increased with higher doses of NSAIDs and in those with comorbidities and the elderly. Patients with a history of GI bleeding, an NSAID-related ulcer, *Helicobacter pylori* infection, renal or hepatic impairment, or chronic heart failure are at increased risk of serious toxicity. Concomitant use of an NSAID with antiplatelet or anticoagulant agents, antihypertensives, glucocorticoids, or diuretics has an additive risk of hemorrhage or renal hypoperfusion. Prior treatment of *H pylori* or concomitant use of a gastroprotectant agent (eg, a proton pump inhibitor) may reduce GI toxicity in those at higher risk.[42] Selective COX-2 inhibitors cause less GI toxicity than nonselective COX-1 and COX-2 inhibitors,[41] but several large studies have shown an increase in cardiovascular toxicity, including myocardial infarction and stroke, with the selective COX-2 inhibitor rofecoxib.[43,44] This is thought to be a result of a prothrombotic effect. Some selective COX-2 inhibitors were withdrawn from the market in 2004 and 2005 because of this toxicity.[44] Celecoxib is one of the main drugs in this class still in common usage.

NSAIDs in Patients With Cancer

The maximum recommended single dose of an NSAID has been found to be equivalent in analgesic potency to approximately 5 to 10 mg of parenteral morphine.[45,46] A meta-analysis of 25 studies in 1,545 patients with cancer found benefit in all eight studies comparing a single dose of an NSAID with placebo.[46] No significant difference in analgesic efficacy was found in studies comparing an NSAID with an NSAID and a weak opioid, but studies were difficult to compare because of heterogeneity (Table 3).

A Cochrane review found seven studies that compared an NSAID (excluding acetaminophen) with placebo for cancer pain.[54] All studies reported improved efficacy for the NSAID, with no difference in adverse effects, but all were single-dose studies. Thirteen studies compared different NSAIDs, but there was no convincing evidence of benefit for one NSAID over another. Of the 10 studies that compared an NSAID with an opioid, four found the NSAID to be more effective, whereas two studies showed they were less beneficial. Meta-analyses of four of the studies found a lack of significant difference in pain relief but more adverse events in the opioid groups (odds ratio, 0.38; 95% CI, 0.15 to 0.97).[45,55-57]

Use of an NSAID With an Opioid

Eight studies compared an NSAID versus an NSAID combined with an opioid; four of these studies found that the NSAID/opioid combination gave marginally better pain relief. Meta-analysis of six of the studies showed no significant difference in adverse events.[54] The studies used a mixture of weak and strong opioids, making comparison problematic.

Both the Cochrane review[54] and a more recent systematic review incorporating additional studies[38] showed a benefit to adding an

Table 2. Illustrative Studies of Acetaminophen (alone or in combination with opioids) in Patients With Cancer

Study	Patient Population				Study Design	Interventions		Results		Comments
	No. of Patients	No. of Patients Analyzed	Type of Pain	Cancer Type		Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/Efficacy	Toxicity	
Axelsson and Borup,[27] 2003	42	30	All	All	Randomized double-blind, cross-over	Acetaminophen (1 g four times a day)/opioid *v* placebo/opioid	7 days in each period	No difference in NRS (0-10)	NA	Written as letter to editor, so minimal detail; large attrition
Stockler et al,[28] 2004	34	30	All	All	Randomized double-blind, cross-over	Acetaminophen 1 g five times a day/opioid *v* placebo/opioid	2 days in each period	Benefit for acetaminophen; mean difference in verbal numeric score (0-10) of 0.4 ($P = .03$)	No difference in adverse effects	Improvement in overall well-being (10-point scale) of 0.7 ($P = .05$); nonsignificant preference for period on acetaminophen, 47% *v* 27%, with 27% having no preference; higher dose of acetaminophen
Tasmacioglu et al,[29] 2009	43	40	Excluded primarily neuropathic pain	All	Randomized, double-blind, parallel	Acetaminophen 1 g IV four times a day/opioid *v* placebo/opioid	1 day	No difference in pain control	No difference	No difference in morphine consumption; used IV acetaminophen and IV opioid (PCA)
Cubero and del Giglio,[30] 2010	50	49	All	All	Randomized, double-blind, parallel	Acetaminophen 750 mg four times a day/opioid *v* placebo/opioid	7 days	No difference in pain control	No difference, except increased somnolence in acetaminophen group	Switched from morphine to methadone ± acetaminophen; acetaminophen did not decrease time to achieve stable methadone dose
Israel et al,[31] 2010	31	22	Excluded primarily neuropathic pain	All	Randomized, double-blind, cross-over	Acetaminophen 1 g four times a day/opioid *v* opioid/placebo	5 days in each period	No difference in pain control; (NRS 0-10) 0.16	No difference	No difference in number of breakthrough doses, 0.42 ($P = .07$); no difference in patient preference; patients on at least 200 mg of oral morphine; large attrition
Sima et al,[32] 2012	246	246	Bone pain	All	Randomized, double-blind, parallel	Oxycodone/acetaminophen (5/325 mg) four times a day/opioid *v* placebo/opioid	3 days	Pain intensity difference benefit for oxycodone/acetaminophen *v* placebo: 1.5 *v* 0.3, respectively, on day 3 ($P < .001$)	5 patients (4%) withdrew from oxycodone/acetaminophen group as a result of adverse events (2 asthenia, 2 dizziness, 1 nausea)	Decreased breakthrough pain in combination group

Abbreviations: IV, intravenous; NA, not applicable; NRS, numerical rating scale; PCA, patient-controlled analgesia.

Table 3. Illustrative Studies of Nonsteroidal Anti-Inflammatory Drugs (alone or in combination with opioids) in Patients With Cancer

	Patient Population					Interventions		Results		
Study	No. of Patients	No. of Patients Analyzed	Type of Pain	Cancer Type	Study Design	Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/Efficacy	Toxicity	Comments
Ferrer Brechner et al,[47] 1984	30	28	All	All	Randomized double-blind, 3-part cross-over	Ibuprofen (600 mg)/methadone (2.5 or 5 mg) *v* methadone/placebo	1 day in each period	Improved pain intensity and pain relief with addition of ibuprofen	No difference	Single dose each day
Lomen et al,[48] 1986	26	22	Bone pain	Breast	Randomized, double-blind, cross-over	Flurbiprofen/opioids *v* placebo/opioids	21 days in each period	No statistically significant difference	No difference	Trend to improvement on flurbiprofen
Stambaugh,[49] 1988	160	160	All	All	Randomized, double-blind, parallel	Ketoprofen (100 or 300 mg) *v* aspirin/codeine (650 mg/60 mg) or placebo	Single dose, follow-up 6 hours	All active arms had improved pain intensity and superior pain relief compared with placebo	No difference	No difference in efficacy between active arms; less rescue medication requirement in ketoprofen groups
Staquet,[50] 1989	126	118	All	All	Randomized, double-blind, parallel	Ketorolac tromethamine intramuscular 20, 30, or 90 mg *v* placebo	Single dose	Ketorolac at each dose superior to placebo	Only minor adverse effects, but 10/15 in ketorolac groups	No difference in efficacy between ketorolac doses; 33 patients withdrawn because of use of rescue analgesics within 6-hour period: 55% in placebo group *v* 23% in ketorolac groups
Carlson et al,[51] 1990	75	70	All	All	Randomized, double-blind, parallel; placebo group randomly assigned to active drug	Ketorolac tromethamine 10 mg *v* acetaminophen/codeine (600 mg/60 mg) *v* placebo	Single dose, then 7 days of one of the active drugs four times daily	Single-dose ketorolac and acetaminophen/codeine superior to placebo; no difference between two active drugs	More adverse effects in ketorolac group (62% *v* 48%)	Multidose small benefit to acetaminophen/codeine
Johnson and Miller,[52] 1994	26	26	Bone pain	Any	Randomized, double-blind, 3-part cross-over	CMT (1,500 mg)/opioid *v* placebo/opioid	3 days in each period	No statistically significant difference	No difference	Trend for improved efficacy with CMT; pain significantly better 1 hour after CMT
Mercadante et al[53] 2002	50	47	Any	Any	Open parallel	Ketorolac (20 mg three times a day)/opioid *v* opioid	Until death	No difference in analgesic efficacy in first 3 weeks	Increased gastric discomfort on ketorolac; increased constipation in opioid only group	Slower opioid escalation in ketorolac group

Abbreviation: CMT, choline magnesium trisalicylate.

NSAID to a WHO step 3 opioid for cancer pain. Five of the seven studies found the addition of the NSAID to be efficacious,[38] with three reporting improved pain with the addition of dipyrone[58] or ibuprofen[47,58a] and two finding a decrease in opioid consumption with the addition of ketorolac[53] or diclofenac.[59] Six of the seven studies reported no significant differences in adverse effects between the groups, with one study finding more gastric discomfort in the NSAID plus opioid arm and more constipation in the opioid alone arm.[53] There were no marked differences between the different NSAID drugs in efficacy, although individual responses to NSAIDs and their toxicity are highly variable.

Most of the acetaminophen and NSAID studies in patients with cancer had small sample sizes and were of short duration, and none included selective COX-2 inhibitors. Longer term efficacy and safety remain unknown, with prevalence and severity of toxicities not quantified in patients with cancer. Studies have not been adequately powered to determine whether NSAIDs or acetaminophen are more beneficial for certain types of cancer pain, although anecdotally, it is suggested that NSAIDs are more effective for pain associated with inflammation.

CORTICOSTEROIDS

Mode of Action

Inflammation has key roles in the pathophysiology of pain, and animal pain models suggest that corticosteroids can modulate pain perception.[18] Proinflammatory cytokines are involved in the development of inflammatory and neuropathic pain, including CNS production from immune-competent glial cells.[18] Endogenous neurosteroids in the CNS and peripheral nervous system modulate γ-aminobutyric acid, *N*-methyl-D-aspartate, and ATP/adenosine bisphosphate (P2X) receptors, all of which play crucial roles in pain regulation.[17] Steroid receptors are present in several neural structures, which may allow steroids to modulate neural activity and plasticity.[17] Sex steroids may also play a role, with testosterone exerting an analgesic effect and estrogens exerting both hyperalgesic and analgesic effects.[17]

Adverse Effects

Corticosteroids have multiple effects and lead to a wide range of potential short- and long-term adverse effects.[19] These include effects on the stress and immune response, carbohydrate metabolism, protein catabolism, electrolyte regulation, and behavior.[19]

Agents and Dose

Commonly used corticosteroids are dexamethasone, methylprednisolone, betamethasone, prednisolone, and prednisone.[18] Dexamethasone is prescribed most often; it causes less fluid retention than other corticosteroids because it has less mineralocorticoid effect.[17,19] Corticosteroids are used with other analgesics in a broad range of clinical scenarios, in particular for management of bone and neuropathic pain.[17] Corticosteroids are included at each step of the WHO analgesic ladder, when an anti-inflammatory effect is considered beneficial.[17] They also have a role in specific clinical scenarios such as spinal cord compression, brain metastases, and bowel obstruction,[60] where improved analgesia is a secondary benefit from the primary indication of reduction of peritumoral edema.[19] There is no established dosing, and the studies that have been undertaken comparing dose effectiveness have explored outcomes other than pain.[61]

Efficacy

Despite corticosteroids being used widely to manage cancer pain, there is limited evidence for their efficacy.[17] A recent systematic review demonstrated a paucity of studies and included four RCTs that explored the role of corticosteroids when added to standard pain management.[18] One study demonstrated efficacy, and one study did not; the other two studies did not report pain or analgesic use adequately[18] (Table 4).

ANTIDEPRESSANTS AND ANTICONVULSANTS

Neuropathic pain is defined by the International Association for the Study of Pain as pain caused by a lesion or disease of the somatosensory system. It is present in at least 35% to 40% of patients with cancer pain.[20] Up to 40% of survivors of cancer also report pain at 5 years after treatment that is often neuropathic in nature.[22] Chronic pain that is related to treatment includes pain caused by postsurgical syndromes (eg, mastectomy, thoracotomy, postamputation); chemotherapy-related painful peripheral neuropathy; avascular necrosis of the femoral or humeral head; and radiation-induced plexopathy, myelopathy, or proctitis.

Opioid analgesia is usually insufficient to achieve good control of neuropathic pain, and additional agents are required, mainly antidepressant and anticonvulsant medications.[20,21] Neuropathic pain from cancer may not share pathophysiologic mechanisms with chronic nonmalignant causes, but a similar range of drugs is used.[21] It is more common to try opioid analgesia alone before adding an adjuvant for neuropathic pain in North America, whereas European practice is to use combination therapy earlier.[22]

Adverse Effects

The choice of agent is often guided by the importance of potential adverse effects in an individual patient. For example, tricyclic antidepressants should be avoided if the patient is at risk of urinary retention. However, some clinicians choose agents based on characteristics of the pain.[21] The agents are used mostly in combination with opioids, and adverse effects, in particular psychoactive adverse effects, can be synergistic.

Agents and Dose

There is a complex interplay between etiology, pathophysiology, and symptoms of neuropathic pain, and different pathophysiologic mechanisms can be responsible for similar symptoms.[66] Therefore, if one agent is not effective, it is reasonable to try another agent that may mediate benefit through a different component of the involved pain pathways. When partial response is seen with one agent, some clinicians consider combination therapy with an agent from another class, but there are few data to indicate additional benefit from combination therapy or to guide the choice of combination.[21] These medications are started usually at a low dose and titrated to a dose where effect is seen with acceptable toxicity. For example, tricyclic antidepressants are started at 10 to 25 mg at bedtime and gradually increased every 3 to 7 days in 10- to 25-mg increments, up to doses of 150 mg.[21] Gabapentin has an effective dose range of 100 to 3,600 mg but is commenced in low doses of 100 to 300 mg at night.[21] Pregabalin doses range from 25 to 600 mg, commencing with 25 to 75 mg at night.[21] Available data suggest that adjuvants improve pain control within 4 to 8 days when

Table 4. Illustrative Studies of Corticosteroids in Patients With Cancer

Study	Patient Population				Interventions			Results		
	No. of Patients	No. of Patients Analyzed	Type of Pain	Cancer Type	Study Design	Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/Efficacy	Toxicity	Comments
Bruera et al,[62] 1985	40	31	All	All	Randomized, double-blind, cross-over	Methylprednisolone 16 mg twice a day/placebo	5 days in each period, 3-day washout	Significant difference	Cushingoid features; anxiety; 3 patients discontinued treatment in methylprednisone arm	Reduced analgesic consumption also reported
Bruera et al,[63] 2004	51	43	All	All	Randomized double-blind, parallel	Dexamethasone 10 mg twice a day/placebo	7 days	No effect on pain or analgesic consumption	Ankle edema; restlessness; 3 patients discontinued dexamethasone	Too low level of pain at baseline may have affected results
Della Cuna et al,[64] 1989	403	198 completed, 142 died	All	All	Randomized double-blind, parallel	Methylprednisolone 125 mg intravenous daily/placebo	8 weeks	Significant difference	Vomiting; hypocalcemia; anemia; hyperglycemia; 10 patients discontinued methylprednisolone (stomach pain, GI bleeding, hypotension, hyperglycemia, hypoalbuminemia)	
Popiela et al,[65] 1989	173	87 completed, 57 died	All	All	Randomized, double-blind, parallel	Methylprednisolone 125 mg intravenous daily/placebo	8 weeks	No significant difference	GI (11%); cardiovascular (8%); 16 patients discontinued methylprednisolone	

added to opioids for cancer pain.[20] The doses used in the randomized studies are listed in Table 5.

Efficacy

There have been two recent reviews (one systematic) exploring the role of pharmacologic therapy of neuropathic cancer pain and another systematic review of the role of antiepileptic or antidepressants added to opioids for cancer pain.[20,21,67] These reviews support a beneficial effect for antidepressants and anticonvulsants in the treatment of both mixed-type and neuropathic cancer pain, but there are methodologic issues with the included studies.[20,21] These include poorly defined primary outcome measures and varying doses of concomitant opioids.[67] In several studies, CIs for outcomes in the intervention arm overlapped with those of the control arm, indicating a lack of significant difference, and it was not possible to make direct comparisons (number needed to treat, number needed to harm) because comparator arms include other active therapies as well as placebo.[67] The effect size seen was much less than that in patients with noncancer neuropathic pain.[20]

There are limited data on treatment that is effective for neuropathic pain related to cancer treatment. A recent RCT explored the use of duloxetine 60 mg, an antidepressant from the selective serotonin and noradrenaline reuptake inhibitor class, for chemotherapy-induced painful peripheral neuropathy; it showed a mean decrease in average pain on an 11-point numeric rating scale of 1.06 (95% CI, 0.72 to 1.4) in the duloxetine group versus 0.34 (95% CI, 0.01 to 0.66; $P = .003$) in the placebo group after 5 weeks of treatment.[69]

BISPHOSPHONATES

Bone metastases, a common source of pain, are caused by upregulated osteoclastic activity, leading to increased bone resorption. Bisphosphonates are selective inhibitors of osteoclastic bone resorption. There are two classes of bisphosphonates—the older simple bisphosphonates, such as etidronate and clodronate, and the more potent inhibitors of bone resorption, the nitrogen-containing bisphosphonates, which include pamidronate and zoledronate. Several meta-analyses have shown a decrease in skeletal-related events with bisphosphonates, and the evidence is strongest for breast cancer,[74] prostate cancer,[75] and multiple myeloma.[76] A Cochrane review reported a reduction in skeletal-related events of 15% (risk ratio, 0.85; 95% CI, 0.77 to 0.94; $P = .001$) in nine studies including 2,806 patients with breast cancer with bone metastases that compared a bisphosphonate with either placebo or no bisphosphonate.[74] A significant improvement in bone pain was found after receiving a bisphosphonate in six of 11 studies that evaluated pain. A meta-analysis of eight studies comparing a bisphosphonate with placebo found minimal differences in adverse events between the two groups, but there was an increase in nausea and acute-phase reactions in the bisphosphonate arms.[75] The risk of osteonecrosis of the jaw is estimated to be between 0.7% and 12% and is more likely to occur in patients with metastatic disease and with poor oral hygiene or after dental surgery[74] (Table 5).

DENOSUMAB

Denosumab is a fully human monoclonal antibody against the cytokine receptor-activated nuclear κB ligand (RANKL), which is involved in tumor cell migration and is a mediator of osteoclast differentiation and activation.[23] Six RCTs in patients with bone metastases found a benefit for denosumab over zoledronic acid, pamidronate, or ibandronate in incidence (risk ratio, 0.84; 95% CI, 0.80 to 0.88) and time to skeletal-related events, but no difference in overall survival,[77] although subgroup analysis in one study suggested that patients with multiple myeloma may have increased mortality with denosumab.[78] Total adverse events were similar, except for increased hypocalcemia and less nephrotoxicity with denosumab. One of the studies, in which pain was a secondary outcome, randomly assigned 2,046 women with breast cancer with bone metastases to denosumab or zoledronic acid. The study reported no meaningful difference in improvement in pain severity or time to improvement of pain between the groups, but there was less worsening of pain severity and less functional impairment secondary to pain and fewer patients required progression to strong opioid analgesics in the denosumab arms[73] (Table 5).

These studies suggest that bisphosphonates are beneficial as an adjunct for pain control from bony metastases for some tumor types. Denosumab is more convenient than bisphosphonates but substantially more expensive.

LIGNOCAINE (LIDOCAINE)

Local anesthetics inhibit pain predominantly by blocking sodium channels and have shown efficacy in chronic nonmalignant neuropathic pain.[21] Topical lignocaine has shown benefit in allodynia from postherpetic neuralgia.[22] There are some uncontrolled and controlled studies of continuous subcutaneous infusion of lignocaine in cancer pain[79-81] (Table 6). However, these studies all have methodologic limitations, and the role of lignocaine needs to be substantiated in randomized placebo-controlled studies.

KETAMINE

The dissociative anesthetic ketamine has been used widely in the management of chronic cancer pain, usually in the setting of pain that is not controlled by opioids or opioids plus adjuvant analgesics.[24] Its use had been mainly extrapolated from surgical settings, and evidence for benefit has come mainly from case series and uncontrolled studies in people with cancer (Table 6). However, in a recent RCT, there was no difference compared with placebo, pain type (neuropathic *v* nociceptive) was not a predictor of response, and those receiving ketamine were more likely to experience adverse effects.[24] This study was not powered to specifically compare differences in effect between neuropathic and nociceptive pain.

CANNABINOIDS

Some cultural groups have used cannabinoids for medicinal purposes for thousands of year. There is a lack of evidence for their efficacy for cancer pain, particularly compared with other agents,[82] but trials are ongoing.

Table 5. Illustrative Studies of Antidepressants, Anticonvulsants, Bisphosphonates, and Denosumab for Analgesia in Patients With Cancer

Study	Patient Population				Study Design	Interventions		Results		Comments
	No. of Patients	No. of Patients Analyzed	Type of Pain	Cancer Type		Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/ Efficacy	Toxicity	
Antidepressants										
Ventafridda V: Psychopharmacology (Berl) 95 Suppl:S44-49, 1988	45	31	Mixed and neuropathic	All	Randomized, double-blind, parallel	Trazodone 75-225 mg/ amitriptyline 25-100 mg	2 weeks	No difference	Not reported	Nonvalidated primary end point
Kalso E: Pain 64:293-302, 1996	20	15	Neuropathic	Post-treatment of breast cancer	Randomized double-blind, cross-over	Amitriptyline 25-100 mg/placebo	4 weeks each with 2-week washout (10 weeks)	Significant difference		No predefined primary end point
Tasmuth T: Eur J Pain 6:17-24, 2002	15	13	Neuropathic pain	Breast cancer	Randomized double-blind, cross-over	Venlafaxine 18.75 mg/ placebo	4 weeks in each period including a dose titration weekly with 2-week washout (10 weeks)	Significant difference		No predefined primary end point
Kautio AL: J Pain Symptom Manage 35:31-39, 2008	42	33	Neuropathic	Receiving vinca alkaloids, platinum, or taxane chemotherapy	Randomized, double-blind, parallel	Amitriptyline 25-50 mg/placebo	8 weeks	No difference in appearance of neuropathic symptoms		Explored prevention
Anticonvulsants										
Keskinbora K: J Pain Symptom Manage 34:183-189, 2007	75	63	Mixed and neuropathic	All	Randomized, open-label, parallel	Opioid plus gabapentin (1,287 mg per day) *v* opioid alone	13 days	Significant difference	Dizziness, sedation	
Caraceni A: J Clin Oncol 22:2909-917, 2004	121	89	Mixed	All	Randomized double-blind, parallel	Opioid plus gabapentin (1,395 mg per day) *v* opioid alone	10 days	Significant difference	Sedation, dizziness, constipation, nausea and vomiting	
Vilholm OJ: Eur J Neurol 15:851-857, 2008	27	25	Postmastectomy pain syndrome	Breast cancer	Randomized double-blind, cross-over	Levetiracetam 1,500 mg twice daily/placebo	4 weeks in each period with 1-week washout (9 weeks)	No difference		
Mishra S: Am J Hosp Palliat Care 29:177-82, 2012	120	120	Neuropathic	All	Randomized double-blind, parallel	Pregabalin 75-300 mg/ gabapentin 300-600 mg/amitriptyline 50-100 mg/placebo	4 weeks	All groups had improvement, with no difference between groups	Somnolence, dizziness, dry mouth, nausea, constipation; no difference between groups	
Rao et al,[68] 2007	115	68	Chemotherapy-induced neuropathy	All	Randomized, double-blind, cross-over	Gabapentin (2,700 mg)/placebo	6 weeks in each period with 2-week washout (14 weeks)	No difference	Mild adverse effects and similar in each group	No intent-to-treat analysis
Rao RD: Cancer 112: 2802-808, 2008	125	80	Chemotherapy-induced neuropathy	All	Randomized, double-blind, parallel	Lamotrigine 300 mg/ placebo	10 weeks	No difference	Mild adverse effects and similar in each group	No intent-to-treat analysis
Yajnik S: J Pain Symptom Manage 7:209-213, 1992	75		Mixed	All	Randomized, double-blind, parallel	Opioid plus phenytoin (100 mg) *v* opioid alone	28 days	Significant difference	3 patients had adverse effects	

(continued on following page)

Table 5. Illustrative Studies of Antidepressants, Anticonvulsants, Bisphosphonates, and Denosumab for Analgesia in Patients With Cancer (continued)

Study	Patient Population				Study Design	Interventions		Results		Comments
	No. of Patients	No. of Patients Analyzed	Type of Pain	Cancer Type		Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/ Efficacy	Toxicity	
Smith et al,[69] 2013	231	141	Chemotherapy-induced pain after taxane or oxaliplatin treatment	Predominantly breast and GI	Randomized double-blind, cross-over	Duloxetine 60 mg *v* placebo	5 weeks	Reduction in average pain at 5 weeks	Fatigue (7%), insomnia (5%), nausea (5%)	Cross-over study but first 5-week period results reported before cross-over
Bisphosphonates										
Lipton et al,[70] 2000	754	751	Bone metastases	Breast cancer	Randomized, double-blind, parallel	Pamidronate (90 mg intravenously)/placebo	Up to 24 months	Pain and analgesic scores significantly better in pamidronate group	Similar rates of adverse reactions between arms; slight increase in hypocalcemia in pamidronate groups	Pain was secondary end point; two studies combined
Body et al,[71] 2004	564	564	Bone metastases	Breast cancer	Randomized, double-blind, parallel	Ibandronate (50 mg oral)/placebo	Up to 96 weeks	Pain and analgesic use significantly better; pain improved within 8-12 weeks of commencing ibandronate	Increased hypocalcaemia in ibandronate groups (9.4 *v* 5.1%) and upper GI symptoms	Pain was secondary end point; two studies combined
Saad and Eastham,[72] 2010	422		Bone metastases	Castration-resistant prostate cancer	Randomized, double-blind, parallel	Zoledronic acid (4 mg) every 3 weeks/placebo	Up to 24 months	Pain significantly better in zoledronate group		Pain was secondary end point
Denosumab										
Cleeland,[73] 2013	2,046			Bone metastases in breast cancer	Randomized, double-blind, parallel	Denosumab (120 mg subcutaneously monthly)/zoledronic acid 4 mg intravenously monthly	18 months	Less worsening of pain, trend to delayed time to pain worsening and less progression to strong opioids with denosumab; no difference in pain improvement	Increased hypocalcemia in denosumab, less nephrotoxicity	Pain was secondary end point

Table 6. Illustrative Studies of Ketamine and Lignocaine for Pain Control in Patients With Cancer

Study	Patient Population			Study Design	Interventions		Results	
	No. of Patients	Type of Pain	Cancer Type		Study Drug/Comparator	Duration of Study Treatment	Pain Outcome/Efficacy	Toxicity
Ketamine								
Hardy,[24] 2012	185	Refractory cancer pain despite treatment with opioids and standard adjuvant therapy at predefined dose levels	All	Randomized, double-blind parallel	No change in baseline opioid or co-analgesic dose was allowed in the 48 hours before study commencement; subcutaneous infusion of ketamine or placebo (normal saline) at three dose levels (100, 300, or 500 mg) in a 5-day schedule with predefined dose titration schedule based on pain score/toxicity	5 days	No significant difference; No. needed to treat, 25 patients	Twice the rate of adverse events worse than baseline, and more severe grade of adverse events in ketamine group; No. needed to harm, 6 patients
Lignocaine								
Sharma et al,[81] 2009	50	Opioid-refractory cancer pain	All	Randomized, double-blind, cross-over	Lidocaine and placebo infusion, separated by 2 weeks		Improved pain	
Bruera et al,[80] 1992	11	Neuropathic pain	Advanced malignancy	Randomized, double-blind, cross-over	Lidocaine 5 mg/kg IV over 30 minutes *v* normal saline over 30 minutes		No difference	
Ellemann et al,[79] 1989	10	Cutaneous allodynia	All	Randomized double-blind, cross-over	Lidocaine 5 mg/kg in 200 mL of 5% glucose IV over 30 minutes *v* 200 mL of normal saline IV over 30 minutes	Infusion over 30 minutes, pain scores up to 1 week	No significant difference	Drowsiness (n = 1); no electrocardiograph abnormalities

Abbreviation: IV, intravenous.

LIMITATIONS OF CURRENT DATA

The evidence for use of nonopioid analgesia in cancer pain remains limited. With the exception of the bisphosphonate/denosumab trials, most studies have small sample sizes, frequently have methodologic limitations, and lack long-term follow-up, so that data on the effects of chronic use of most of the agents remain limited.

RECOMMENDATIONS FOR FUTURE RESEARCH

Some of the outstanding questions include the following: whether acetaminophen should be used concurrently with an opioid and, if so, in what dose; whether NSAIDs and corticosteroids can be safely continued long term in patients with cancer and the safety and efficacy of the selective COX-2 inhibitors still on the market; and which nonopioid analgesics are best for specific types of pain and in which combinations. Pharmacogenomics and phase IV studies may have a role to play in answering these questions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
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