International Association for the Study of Pain
IASP
Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 49
Profiles, Doses, and Side Effects of Drugs Used in Pain Management

Barbara Schlisio

The following drug list is a selection of commonly used drugs for pain management. The selection reflects recommendations of the "Essential Drug List for Cancer" from Makarere University and the health ministry in Uganda for the treatment of cancer patients, which appear to be a reasonable drug selection for treatment of the most common pain syndromes encountered by nonspecialists in a low-resource setting.

This overview explains the mode of action as well as typical side effects of drugs. "Typical side effects" means that other side effects have been described, but I have selected from the lengthy lists of side effects mentioned in desk references the ones that are most important for the therapist and the patient to know about.

Pharmacological therapy in pain management is often selected because of positive empirical knowledge, because most of the time there are no controlled studies of high methodological quality. This means that safety is an issue to be considered when selecting a drug: the possible positive effects must always be balanced against possible side effects. A good recommendation would be to think, when prescribing a drug, whether you would prefer the same drug when in a comparable situation, since it is your decision to select pharmacological treatment.

Pharmacological treatment should be explained thoroughly to the patient, and "informed consent" should be obtained in the same way as for a surgical intervention. A valuable tool to avoid misunderstandings and "incompliance" by the patient is the use of a simple (makeshift) "information sheet" to be given to patients when they leave the office with their prescription.

Here is an example of an information sheet to give to patients:

Name of Drug	How to Take It	What Is It For ?	Important Information
Morphine	1 tablet of 20 mg: 6–12–18–24 o'clock	Strong painkiller for continuous pain control	Nausea and tiredness are possible the first week. Never change the dose on your own!
Morphine	1 tablet of 10 mg as needed	Strong painkiller to be taken if pain increases	See above. Minimum time between extra morphine tablets: 30 minutes.
Metoclopramide	40 droplets: 6–12–18–24 o'clock	Prevents nausea caused by morphine	Should be taken for 10 days. After that, try to go without it.
Carbamazepine	1 tablet of 200 mg: 8–16–24 o'clock	Helps against shooting nerve pain	Dizziness and tiredness in the first few days or weeks. Remember to come to the office to have a blood sample taken in one week.

Guide to Pain Management in Low-Resource Settings, edited by Andreas Kopf and Nilesh B. Patel. IASP, Seattle, © 2010. All rights reserved. This material may be used for educational and training purposes with proper citation of the source. Not for sale or commercial use. No responsibility is assumed by IASP for any injury and/or damage to persons or property as a matter of product liability, negligence, or from any use of any methods, products, instruction, or ideas contained in the material herein. Because of the rapid advances in the medical sciences, the publisher recommends that there should be independent verification of diagnoses and drug dosages. The mention of specific pharmaceutical products and any medical procedure does not imply endorsement or recommendation by the editors, authors, or IASP in favor of other medical products or procedures that are not covered in the text.

Nonopioid analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Despite their chemically differences, NSAIDs have a common mode of action, the inhibition of prostaglandin synthesis by the cyclooxygenase isoenzymes COX-1–3. Remember that prostaglandins sensitize peripheral nociceptor nerve endings to mechanically and other stimuli, thus provoking a decreased pain threshold. Centrally active prostaglandins enhance the perception and transmission of peripheral pain signals. But NSAIDs do interfere with a number of other physiological functions as well, which explains most of their side effects. These unwanted effects include the release of gastric acid, the aggregation of platelets, the activity of vascular endothelium, the initiation of labor, and an influence on the ductus arteriosus of neonates.

NSAIDs are usually indicated for the treatment of acute or chronic pain conditions, especially where inflammation is present. In pain of low to moderate intensity, they may give sufficient pain control as a single therapy, but in moderate to severe pain they should only be used in combination with opioids. In the postoperative situation it makes especially good sense to combine opioids and NSAIDs because the reduction in the dose of opioids will reduce any opioid side effects. Different NSAIDs are available in different countries. Diclofenac and ibuprofen are used most frequently, but other NSAIDs have been shown to be comparable. To avoid unintended drug accumulation, certain long-acting NSAIDs should be avoided (e.g., piroxicam), and to avoid gastrointestinal and renal side-effects, all NSAIDs should be used short-term only. Most NSAIDs cause ulcers and other upper gastric symptoms such as dyspepsia and epigastric pain or discomfort if used long-term (>7–10 days). A less common but serious side effect is anaphylactic reaction with development of severe bronchospasm and/or cardiovascular depression. Renal failure is a more frequent and serious complication and is mostly associated with long-term use, especially in patients with a history of previous renal impairment and hypovolemia.

Note the contraindications: gastrointestinal ulceration, hemophilia, hypersensitivity to aspirin, young children because of the possibility of developing Reye's syndrome, pregnancy especially the last trimester, breastfeeding, and advanced renal impairment.

The standard dose of diclofenac is 50–75 mg t.i.d. (three times a day), of ibuprofen 400–800 mg t.i.d., and of aspirin 500–1000 mg q.i.d. (four times a day).

Acetaminophen (paracetamol)

The exact mechanism of action is unclear. Acetaminophen might inhibit a central cyclooxygenase isoenzyme (COX-3) and act as a central and spinal substance P inhibitor. Even though acetaminophen is classified as an antipyretic drug, it has mild anti-inflammatory properties. Acetaminophen is a safe alternative medication when NSAIDs are contraindicated or not well tolerated by the patient.

Acetaminophen is well tolerated in therapeutic doses, but it is hepatotoxic at high doses (approximately 6–15 g per day), when its metabolites can produce fatal liver necrosis. Alcohol-dependent and undernourished patients are at especially high risk. Renal tubular necrosis may also occur. However, and rightly so, acetaminophen is often used for minor to moderate pain postoperatively, as well as in headache and cancer patients, because it is free of any gastrointestinal and renal side effects when the dose recommendations are observed.

Note the contraindications: severe hepatic and renal impairment, alcohol-dependent patients, undernourished patients, and patients with glucose 6-phosphate dehydrogenase deficiency.

The standard dose of paracetamol is 500–1000 mg t.i.d., and postoperatively the initial oral or rectal dose should be 2000 mg.

Dipyrone (metamizol)

Dipyrone is supposed to be a central cyclooxygenase inhibitor. It acts as an antipyretic. It differs from other nonsteroid drugs in respect to its spasmolytic effects, since dipyrone inhibits the release of intracellular calcium. The benefits of dipyrone are that you do not have to worry about renal function and gastrointestinal side effects and that it is generally cheap. Like acetaminophen, dipyrone may also be used for long-term treatment. Its indications are acute and chronic pain of mild to moderate intensity, as well as colicky pain.

A number of patients will complain about sweating, for which there is no tolerance. The topic of idiosyncratic drug reactions has been reopened after some Scandinavian publications, and a number of countries have therefore made dipyrone unavailable. But several countries, including Germany, Spain, and most Latin American countries, consider the risk low, compared to

the side effects of NSAIDs. Rapid intravenous application may be associated with hypotension, which should not be mistaken for a allergic response, which in fact occurs only rarely. Contraindications include porphyria, glucose-6-phosphate dehydrogenase deficiency, pregnancy (especially the last trimester), and breastfeeding.

The standard dose of dipyrone is 500–1000 mg q.i.d.

Opioid analgesics

For legal reasons, opioids may be classified into weak and strong ones. The World Health Organization (WHO) three-step ladder for cancer pain management also follows this distinction, advocating first the use of a "weak" opioid (e.g., tramadol or codeine) followed by a "strong" opioid (e.g., morphine or hydromorphone). For clinical practice, this distinction is probably irrelevant, because there are no data indicating that equianalgesic doses of "weak" and "strong" opioids have a different side-effect or effectivity profile. Therefore, opioid therapy may be started with low doses of a "strong" opioid, if "weak" opioids are not available.

Opioids may also be classified according to their receptor affinity. The analgesic effect of opioids is mediated through binding to μ, κ, and δ receptors. With the exception of pentazocine, tramadol, and buprenorphine, all commonly available opioids are more or less pure μ-agonists with a linear dose-effect function. Tramadol, pentazocine, and buprenorphine on the other hand have a ceiling effect, and they bind to different or additional receptors. Opioid receptors are found in several areas of the brain, the spinal cord and—contrary to common belief—in the peripheral tissues, especially if inflammation is present. The analgesic effect is a result of the reduced presynaptic opening of calcium channels and glutamate liberation as well as the increase of postsynaptic potassium outflow and hyperpolarization of the cell membrane, which reduces excitability.

Treatment with opioids involves a balance between sufficient analgesia and the typical side effects. Luckily, the most frequent side effects—nausea, respiratory depression, and sedation—diminish over time because of tolerance, and constipation may be prophylactically treated with good results.

The best clinical indications for opioids are the symptomatic treatment of moderate to severe acute pain, especially postoperative pain and cancer pain. Neuropathic pain may be an indication, too, especially in HIV/AIDS patients. Unfortunately, chronic noncancer pain, like chronic nonspecific back pain or headache, is only rarely a good indication for opioids. In palliative care, opioids may also be used to control dyspnea very effectively.

Drug abuse with opioids is extremely rare in patients who do not have a history of alcohol, benzodiazepine, or opioid abuse! The reason is that when opioids are used for control of pain, the regular dosing avoids major changes in serum levels, therefore preventing the activation of our dopaminergic reward system (as opposed to drug addicts experiencing a "high" after sudden blood level increases after the intravenous push-injection of an opioid and a "craving" in the time interval before the next injection). Do not confuse drug addiction with physical dependence. As a matter of fact, all opioids cause physical dependence (as with a number of other classes of drugs, such as beta blockers or anticonvulsants), and patients will develop symptoms of withdrawal if they discontinue opioids without tapering down the dose.

"Weak" opioids

According to the three-step ladder of the WHO for cancer pain, weak opioids should be used first, if nonopioid analgesics are insufficient to control the pain. Tramadol, codeine, and dihydrocodeine are examples of this group. Tramadol has affinity to the μ-opioid-receptor, as well as reuptake inhibiting activities for norepinephrine and serotonin in the descending inhibitory nervous system. Tramadol is also thought to have some NMDA-receptor antagonist effects. Weak opioids are sometimes available in fixed combinations with NSAIDs or acetaminophen/paracetamol.

Weak opioids, unlike strong opioids, have a ceiling effect, meaning that there is a maximum dose above which there is no further increase of analgesia. The risk for respiratory depression is very low with weak opioids. Depending on the region of the world where tramadol or codeine are used, certain genetic polymorphisms may exist that can result in the need for unexpectedly high or low doses. For example, in Eastern Asia and Northern Africa, hepatic metabolism of codeine and tramadol may be impaired in a considerable proportion of the population. Otherwise, the drugs are considered very safe, even in patients with impaired organ function.

The standard dose for tramadol is 50 to 100 mg t.i.d., which is sufficient for postoperative analgesia after most surgical interventions. Tramadol is also available in an intravenous application formulation.

"Strong" opioids

Strong opioids are the medication of the first choice in severe pain in cancer and postoperative pain as well as in cancer-related dyspnea. They may also work to a lesser extent in neuropathic pain, but they are generally not indicated for use in chronic nonspecific pain, such as headache, chronic back pain, fibromyalgia, or chronic irritable bowel syndrome. Do not hesitate to use strong opioids early enough in cancer pain, because they can improve the patient's quality of life remarkably. There is no maximum dose for morphine and its derivates. As a result of progress of the illness, patients often—but not always—require an increase of the dose over the course of the disease. Dose increases do not mean tolerance or addiction, but reflect progressive tissue damage most of the time. Other causes of increasing dose demands are a change in pain quality (development of neuropathic pain instead of nociceptive pain) or concomitant anxiety or depressive disorders. The other causes mentioned have to be diagnosed correctly to be able to treat them specifically with coanalgesics or nonpharmacological interventions.

Nausea and vomiting, drowsiness, dry mouth, miosis, and constipation occur very frequently in patients taking strong opioids. If nausea and vomiting persist, or delirious symptoms develop, a change to another opioid ("opioid rotation") usually controls the problem. Constipation will occur in all opioids and requires therefore constant prophylaxis, while antiemetic drugs should be used prophylactically for only a short period of time (7–10 days), until tolerance has developed. Consider, and explain to the patient, that opioids are not toxic to any organ. Hence there are no contraindications, except in patients with a history of allergic reactions (very rare). Other contraindications such as chronic obstructive pulmonary disease or renal function impairment do not mean that opioids should be withheld, but that their dose must be titrated slowly and carefully to effect.

Strong opioids may even be used in pregnancy, but close cooperation with the pediatrician or neonatologist is necessary to cope with respiratory depression and/or opioid dependency in the neonate.

Dependency occurs in most patients when more than about 100 mg of morphine is given daily for more than 3 weeks. To avoid withdrawal syndrome, the patient must be instructed never to just stop taking the opioid medication but to follow the physician's instructions. A safe protocol would be to taper down the dose in several steps over about 10 days, which safely prevents withdrawal syndromes (tearing, restlessness, tachycardia, and hypertension, among other symptoms).

The starting dose for morphine is approximately 20–40 mg orally per day, four times a day (q.i.d.). If slow-release formulations are available, once- or twice-daily doses may be chosen. When only immediate-release and slow-release formulations are available, a fixed schedule of opioid medication should be combined with an on-demand dose, which should be approximately 10–20% of the cumulative daily opioid dose. For example, in a patient taking 20 mg morphine q.i.d. (80 mg daily consumption), 10 mg of morphine should be allowed as an extra dose to be taken on demand in situations of increased pain ("breakthrough pain"). The patient should observe a minimum time interval of 30 to 45 minutes before using another demand dose. According to the number of daily demand doses, the caregiver may change the constant basal dose of morphine. In a patient needing no demand doses at all, the basal dose may be reduced by 25%, in a patient requiring one to four doses the scheme should stay unchanged, and in a patient requiring more than four demand doses the basal opioid dose should be increased. For example, in a patient with a basal morphine dose of 4 times 20 mg of morphine requiring on average daily 6 times 10 mg of morphine on demand, the basal dose of morphine should be increased to 4 times 30 mg (and the demand dose should be increased to 20 mg).

The same approach should be used for the treatment of dyspnea (even in patients not suffering from pain). Opioids decrease the "breathing force" by a rightward shift of the CO_2 response curve, effectively reducing the subjective "air hunger."

All pure μ-opioid agonists are interchangeable and combinable and differ only in their subjective side-effect profile (which is not predictable individually) and in their relative potency (not their absolute potency). The equianalgesic doses for 10 mg morphine orally are 2 mg hydromorphone, 5 mg oxycodone, 100 mg of tramadol, and 1.5 mg of levomethadone.

The equianalgesic doses of all opioids depending on the application route must be known. In morphine, these are:

Equianalgesic doses of morphine	
Intravenous (i.v.) Subcutaneous (s.c.) Intramuscular (i.m.)	10 mg
Oral	30 mg
Epidural	2–3 mg
Intraspinal	0.1–0.3 mg

Transdermal opioids

Two patches are now available for the delivery of opioids—the fentanyl patch and the buprenorphine patch. These drugs are strongly lipophilic, allowing good passage through the skin into the circulation and avoiding first-pass metabolism in the liver. Consider that analgesia and side- effect profile do not change by using the transdermal route. Therefore, only patients with swallowing problems or recurrent vomiting would benefit from this route of application. If transdermal systems are used, remember that they are indicated only in patients with stable opioid requirements and that it takes around half to one day for the patch to produce a steady state of opioid delivery to the patient (and the same time for blood levels to decrease if the patch is taken off). In conclusion, the vast majority of patients in cancer and palliative care may be treated well with opioids without the use of transdermal systems (which are also considerably more expensive!).

Adjuvant medications for opioid-related side effects

Nausea, vomiting, and constipation associated with opioids need a concomitant "adjuvant" medication. Without one, your patients' compliance will be low! For the first week of opioid therapy, metoclopramide 10 to 30 mg q.i.d. should always accompany the opioid. As mentioned above, earlier tolerance to the nauseating side effects of opioids will then develop. Sedation must to be explained to the patient, since there is no effective adjuvant medication to counteract it. For constipation, a constant prophylactic laxative therapy must be initiated immediately with the start of an opioid. Milk sugar or bisacodyl are good choices. See the chapter on constipation for further details on this therapeutic problem.

Coanalgesics

Coanalgesics are drugs that were originally developed for purposes other than analgesia, but were then found to be useful in certain pain states. Their use is common in neuropathic pain, where NSAIDs and antipyretics are ineffective most of the time and opioids often fail to be effective.

Although a number of substances have shown to have "coanalgesic" properties (among others: capsaicin, mexiletine, amantadine, ketamine, and cannabis), only antidepressants, anticonvulsants, and steroids are used regularly and are most likely to be available in low-resource settings. The use of coanalgesics necessitates knowledge of how to balance benefits and risks and avoid side serious side effects.

As with opioids the doses of most coanalgesics have to be titrated to the effect, meaning, that the dose recommendations for their original indications cannot be transferred to the indication "pain". As always when treating pain, use thorough patient education to gain good patient compliance and adjust and readjust doses and drug selection to gain the best results for your patients. Don´t forget to give a message of hope to your patient but be honest with him and set realistic goals: coanalgesics will not take away the pain, but will only be able to give some relief!

Anticonvulsants

They reduce neuronal excitability and suppress paroxysmal discharge of the neurons by stabilizing neural membranes. Anticonvulsants work by interacting with different mechanisms, e.g., the voltage dependent sodium channel or by the high voltage calcium channels. Anticonvulsants of the sodium channel blocking type (carbamazepine, oxcarbazepine or lamotrigine) show best results in attack like shooting pain, e.g., in patients, where the cancer has infiltrated nerve plexus or in trigeminal neuralgia. Anticonvulsants of the calcium channel blocking type (gabapentin, pregabalin) are indicated above all for continuous burning pain, e.g., in patients with polyneuropathies or postherpetic neuralgia. The latter seem to have a synergistic effect on the calcium channels with opioids. Phenytoin can be used as a "rescue" substance for severe and therapy resistant neuropathic pain. All anticonvulsants should be titrated according to the rule "start low, go slow". Recommended dose ranges for the most common anticonvulsants in pain management are:

Substance	Starting Dose	Maximum Dose	Remarks
Carbamazepine	3 × 100 mg	1600 mg/day	A low dose is often effective
Oxcarbazepine	3 × 150 mg	2250 mg/day	There is less dizziness and sedation
Gabapentin	3 × 100–300 mg	3600 mg/day	A high dose is often required
Pregabalin	2 × 25 mg	300 mg/day	Has anxiolytic effects
Phenytoin	1 × 100 mg	400 mg/day	Avoid long-term use

All anticonvulsants produce drowsiness and dizziness, although this problem can be minimized by increasing the dose slowly, every 4 to 8 days depending on the individual side-effect tolerance. In carbamazepine and oxcarbazepine, regular blood tests (e.g., weekly for 4 weeks, then monthly for 3 months, and then once every 3 months) are necessary to identify patients with elevation of liver enzymes, idiosyncratic drug reactions, and hyponatremia. Idiosyncratic drug reactions denote a non-immunological hypersensitivity to a substance, without any connection to pharmacological toxicity. The medication has to be stopped in all cases of idiosyncratic reaction, if liver transaminases are above ca. 200 and if sodium is below 125. The same applies to phenytoin (with the exception of the danger of developing hyponatremia), for which a normal ECG (look especially for AV-conduction abnormalities) should also be a prerequisite. For gabapentin and pregabalin, no blood tests or ECG controls are necessary. Contraindications for all anticonvulsants include porphyria, lactation, myasthenia gravis, glaucoma, and chronic renal or hepatic failure.

Antidepressants

Antidepressants were the first coanalgesics used after it was found that they effectively reduced pain in polyneuropathy, even in patients who were not depressed. They have been found to be effective in the treatment of constant burning neuropathic pain of different origins. Furthermore, antidepressants are also useful in treating tension type headache and as a prophylactic treatment in migraine headache. Contrary to common belief, there is no "general pain-distancing" effect, so antidepressants should only be used for the indications named above. As a general rule, the "classical" tricyclic antidepressants are the most effective in pain management. Although the best evidence exists for amitriptyline, all tricyclic antidepressants are considered equally effective. The newer and more tolerable selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are less potent or not effective, unfortunately. The only SNRIs considered to be effective in the latest meta-analysis are venlafaxine and duloxetine.

Antidepressants induce analgesia by increasing the neurotransmitters serotonin and norepinephrine in the descending inhibitory nervous system (e.g., in the periaqueductal gray). Additionally, antidepressants modulate the opioid system in the central nervous system. Some side effects can be used for the benefit of the patient, such as the sedating effect of amitriptyline for better sleep and the anxiolytic effect of clomipramine for relaxation. If the patient is in an advanced stage of disease with impaired general condition or comorbidities, nortriptyline and desipramine seem to be safer alternatives to use within the class of tricyclic antidepressants.

As with anticonvulsants, the effective dose has to be titrated individually using the rule "start low, go slow" to avoid debilitating side effects. All tricyclic antidepressants should be started with a dose of 10 mg at nighttime, and the dose should be increased every 4–8 days by only 10–25 mg daily.

Elderly patients should not be medicated with tricyclic antidepressants because of multiple drug interactions and an increased rate of falls. For all other patients it has to be remembered that the analgesic effect often starts after a delay, and therefore the caregiver as well as the patient have to have some patience before deciding whether the treatment is effective.

The most frequent side effects are due to the anticholinergic properties of antidepressants (mostly of the tricyclic class) via the muscarinic receptors. Such anticholinergic effects include xerostomia (dry mouth), constipation, urinary retention, blurred vision and impaired accommodation, tachycardia, and slowed gastric emptying. Explain to patients that they are receiving the medication for pain, since they might read the package explanation, where "depression" is the only indication. Also let the patient know that sedation and most other side effects usually wear off over several weeks. Explain that these medications relieve pain but do not resolve it.

Because tricyclic antidepressants may impair liver function, it is advisable to check the liver enzymes regularly (e.g., once a month for 3 months and than once every 3 months). Before initiating tricyclic antidepressant medication, check the ECG for major AV node irregularities and polytope extrasystoles.

Up to 20% of cancer patients develop episodes of depression, and in this case antidepressants with the lowest side effects should be used (SNRIs and SSRIs).

Steroids

Steroids are widely used in cancer pain therapy, especially in patients with an advanced stage of disease. These agents reduce perineural edema and may inhibit spontaneous activity in excitable, damaged nerves due to cancerous infiltration or compression of nerval structures. Because of their anti-inflammatory effects, steroids may be also used in chronic inflammatory diseases, such as rheumatoid arthritis. In cancer patients the drug of choice is dexamethasone, which provides only glucocorticoid properties, causing less fluid retention and potassium loss as compared to hydrocortisone or prednisolone. There is no evidence-based dosing scheme, but in acute pain exacerbation because of massive cancer progression, a common approach would be to use a loading dose of approximately 24 mg the first day and then reduce the dose subsequently over the following days to a maintenance dose of 2 mg daily.

Side effects can prove to be beneficial for the patient, such as euphoria and an increased appetite in cachectic patients. "Negative" uncommon side effects may include psychotic episodes and myopathies. Other typical side effects such as osteoporosis, skin thinning, diabetes, and adrenal suppression are of less importance in the target patient with limited life expectancy. To limit the risk of gastric ulcers, do not combine NSAIDs and steroids, and do not use steroids unless critical in the noncancer patient.

Neuroleptics

Neuroleptics are psychoactive drugs that are commonly used to treat psychotic episodes and nausea. Patients with advanced cancer often suffer from delirium. Do not underestimate the distress for the patient and family in the presence of delirium. Try to identify the reason for the delirium. Most of the time it is the first sign of infection, renal failure, dehydration, or electrolyte imbalances. In rare instances, it may also be a side effect of opioid therapy (in which case, opioid rotation will solve the problem). Always identify and treat the underlying cause along with giving symptomatic treatment with neuroleptics (titrate in increments of 2.5 mg to effect with haloperidol with a "normal" daily dose of 2.5 to 5 mg t.i.d.). In advanced cancer patients, delirium may also be a sign of reaching the terminal stage ("terminal disorientation"). Even at the final stage of illness, delirium should be treated, to reduce the stress of the patient and family.

Neuroleptics (like benzodiazepines) have no analgesic efficacy and therefore should never be used for the indication of pain. Pain needs analgesics and not sedation, with the exception of terminal sedation, when all available alternatives for pain control fail.

Note also that neuroleptics are potent blockers of D_2 receptors in the dopamine pathways of the brain. Therefore, they have direct effects on opioid-induced nausea and are very valuable antiemetics (a dose of 0.5 to 1 mg of haloperidol t.i.d. is sufficient for that purpose and is without psychomimetic effects).

Other neuroleptics that may be available include thioridazine (25 to 50 mg daily), chlorpromazine, and levopromazine. They all have a low neuroleptic potency, but a good sedating effect, and therefore may be used as sleeping pills in cancer patients. The new "atypical" neuroleptics such as olanzapine or risperidone are not the first choice for cancer patients and should be reserved for patients with psychiatric disorders.

Antipsychotics are associated with a wide range of side effects. Extrapyramidal reactions include acute dystonia, tardive dyskinesia, and Parkinson-like symptoms (rigidity and tremor) due to blockage of dopamine receptors. Tachycardia, prolonged QT interval, hypotension, impotence, lethargy, seizures, and nightmares are possible. Another serious side effect is neuroleptic malignant syndrome. In this case the temperature regulation centers fail, resulting in a medical emergency, as the patient's temperature suddenly increases to dangerous levels. Most of the above-mentioned side effects are fortunately rare and not of relevance in the period of the end of life.

Benzodiazepines

Benzodiazepines are a group of drugs with varying sedative, anxiolytic, anticonvulsant, and muscle relaxant properties. The main indication for these drugs in pain management and the palliative care management is the treatment of anxiety and intractable dyspnea. Do not hesitate to prescribe these drugs for terminal

ill patients, who suffer from panic attacks, dyspnea and insomnia. Benzodiazepines are highly beneficial in the palliative care setting.

Benzodiazepines bind at the interface of the α and γ subunits on the γ-aminobutyric acid (GABA) receptor, the most prevalent inhibitory receptor within the entire brain. The anticonvulsant properties of benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels.

Benzodiazepines are well-tolerated and safe. If you want to treat panic attacks, use benzodiazepines with shorter half-lives, such as lorazepam. Diazepam has a long half-life. Diazepam can be administered orally, intravenously, intramuscularly, or as a suppository. The dose is between 2 and 10 mg as a single dose or twice daily. Sometimes it is necessary to increase the dose extensively without negative consequences. Diazepam, in combination with morphine, is the drug of first choice for palliative sedation. For trait anxiety in terminal illness, flunitrazepam subcutaneously once daily is a very effective choice (normally in a dose range between 0.5 and 5 mg).

During the course of therapy with benzodiazepines, tolerance to the sedative effects usually develops, but not to the anxiolytic effects. Diazepam does not increase or decrease hepatic enzyme activity. There is no real contraindication in the palliative setting if used with care, titrated to effect, and used where indicated.