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Pharmacologic Treatment of Chronic Pain

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LEARNING OBJECTIVES

1. Identify and differentiate between the signs and symptoms of nociceptive and neuropathic pain.
2. Describe the benefits and limitations of COX-1 and COX-2 inhibitors.
3. Compare and contrast various opioids used in chronic pain management.
4. Demonstrate the ability to be able to convert opioid parenteral forms to oral forms.
5. Compare and contrast the therapeutic options in treatment of chronic neuropathic pain.

ABSTRACT: An estimated 48 million Americans suffer from chronic pain. More than 4 out of 10 patients in routine practice settings fail to receive adequate treatment. The undertreatment of pain is a major issue in today's society. Undertreatment of pain is complicated by a health care professional's fears of a patient's addiction and diversion and regulatory action by the Drug Enforcement Agency (DEA). Effective pain management includes determining the underlying cause of pain, performing a physical assessment, using a pain scale, and classifying the type of pain. Three major classifications of pain are neuropathic, nociceptive, and idiopathic. Each class of pain varies in characteristics, etiology, onset of symptoms, and response to various medications. This article discusses in-depth, current treatment options in treating chronic pain, which includes opioids, tricyclic antidepressants (TCAs), antiepileptics, *N*-methyl-D-asparate (NMDA) receptor antagonists, and antiarrhythmic agents. An in-depth analysis of doses, various dosage forms, mechanisms of action, relative efficacy, adverse reactions, and drug interactions of the medications listed above will be discussed.

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PHARMACOLOGIC TREATMENT OF CHRONIC PAIN

Numerous articles have been written about the undertreatment of pain owing to a health care professional's fears of addiction, patient diversion, regulatory action by the DEA, respiratory depression, and tolerance.[1] Bill McCarberg, M.D., Director of Pain Services, wrote in a July 2002 issue of *Managed Care* about the consequences of these fears and the legal ramifications. In 1990, in North Carolina, regarding the case of the Estate of Henry James v. Hillhaven Corp., a jury awarded $15 million to the family of a deceased patient who had prostate cancer. His last days were made intolerable by a decision made by a nurse and her employer to withhold or reduce pain medication ordered by the patient's physician. The physician had prescribed oral morphine elixir every 3 hours as needed for pain, but the nurse determined that the patient—who was not expected to live more than 6 months when he was admitted to the nursing home—was "addicted to morphine." She therefore substituted a mild tranquilizer and delayed or withheld the administration of analgesics. With a better understanding of medications used to treat pain, a health care professional's fears and a patient's pain can be better managed.[2]

One of the most common reasons patients visit health care facilities is because of pain. An estimated 48 million Americans suffer from chronic pain, and according to American Pain Society, more than 4 out of 10 patients in routine practice settings fail to receive adequate treatment. Since pain is subjective, treatment is complicated with issues of both biologic and psychologic facets. The adverse psychologic effects from pain include anger, anxiety, appetite suppression, depression, interference with sexual activity, and sleep deprivation, all of which markedly erode the quality of life for the patient.[3] All the effects of pain must be addressed to treat the patient effectively.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[4] Pain can be classified according to location (site of injury), intensity, underlying cause, frequency, and duration.

The location or site of injury aids in establishing the optimal formulation of medication to be dispensed. For example, the site of injury may be external or internal; for the former, a topical medication, such as an ointment, should be applied; or for the latter, an oral medication, such as an antibiotic, should be dispensed.

With multiple medications for pain control available, the intensity of pain the patient is experiencing helps narrow the margin of possibility. Intensity (or severity) of pain may be described through various parameters such as pain scales, the patient's vital signs (blood pressure, pulse, respiration, and temperature), assessment of the tissue damage, and the patient's own description.[5] Lastly, pain is complicated by a patient's diverse beliefs, such as some patients believe that tolerating excessive pain is a sign of strength; they agree with the government's campaign, "Just Say No to Drugs," or the negative

stigma associated with the use of narcotics and addiction held by the media.[6]

Underlying causes, frequency, and duration determine whether the pain is acute or chronic, malignant or nonmalignant, neuropathic, somatic, or visceral. Acute pain is considered to be for less than 30 days, and chronic pain is considered to be longer than 3 months. Chronic pain does not exhibit acute pain behaviors, yet is often associated with affective disorders such as sleep disturbances, anxiety, and depression. Some examples of acute pain are dysmenorrhea, labor pain, and postoperative pain, whereas examples of chronic pain are Multiple Sclerosis, AIDS/HIV, burns, and fibromyalgia.[3,4]

Pain classifications include the following:[7]

- *Neuropathic pain* is the result of damage to afferent fibers (either in the peripheral or central nervous system) that causes a constant firing of the affected nerve fibers, which lead to the patient experiencing painful sensations. It is often described as sharp, burning, numbing, radiating, shooting, and/or stinging severe pain that is poorly localized, but is usually in the extremities and spine. It typically does not appear until weeks or months after an initial injury to the nervous system (i.e., peripheral neuropathy or trigeminal neuralgia).

- *Nociceptive pain* is initiated by a potentially detrimental or damaging (noxious) stimulus caused by mechanical changes, chemical changes in the environment or body, or excessive changes in temperature, which elicits tissue destruction. It is subdivided into 2 categories: somatic and visceral pain. Somatic pain is often described as dull, aching, gnawing, throbbing pain that is well localized (originating from the skin, bones, or muscles). Examples of somatic pain are bone metastases, musculoskeletal pain, or soft tissue metastases. Visceral pain is characterized by deep, pressure-like squeezing, radiating pain that is poorly localized (coming from the abdominal or thoracic organs) and can be associated with diaphoresis, nausea, and vomiting. Examples of visceral pain include involuntary muscle pain, liver metastases, and pancreatic cancer.

- *Idiopathic pain* is non-specific pain of unknown origin. Stress, anxiety, and depression can influence this type of pain, which is usually located in the head, neck, shoulders, abdomen, and pelvic areas. An example of idiopathic pain is fibromyalgia.

PAIN TRANSMISSION

According to Ganong, in *Review of Medical Physiology*, under the section Physiology of Nerve and Muscle Cell, Synaptic Junction and Transmission, "Nerve endings have been called biologic transducers that convert electrical energy into chemical energy. In broad terms, this conversion process involves the synthesis of the transmitter

agents, their storage in synaptic vesicles, and their release by the nerve impulses into the synaptic cleft. The secreted transmitters then act on appropriate receptors on the membrane of the postsynaptic cell and are rapidly removed from the synaptic cleft by diffusion, metabolism, and, in many instances, reuptake into the presynaptic neuron. All these processes, plus the postreceptor events in the postsynaptic neuron, are regulated by many physiologic factors and, at least in theory, can be altered by drugs."[8]

TREATMENTS FOR CHRONIC NOCICEPTOR AND NEUROPATHIC PAIN

Nociceptor Treatments

Nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, are the most widely used medications, both prescription and over the counter, in the United States.[9] NSAIDs have analgesic, anti-inflammatory, as well as antipyretic properties, are used in mild-to-moderate pain, are categorized in Step I of the World Health Organization (WHO) program for cancer pain relief, and are useful in treating bone pain and arthritis. Other non-opioid analgesics such as aspirin and acetaminophen are used in combination products such as oxycodone and hydrocodone to treat moderate-to-severe pain.[10] Limitations of these medications are attributable to their "ceiling effect" (a maximum daily dose, above which there will be no increase in analgesia, but there will likely be an increase in adverse effects) and side effect profile. For instance, in order to prevent dose-dependent hepatotoxicity acetaminophen should not exceed 4 to 6 grams per day.[4,5] Patients with cancer are not often given aspirin because of the high incidence of gastropathy and aspirin's ability to inhibit platelet aggregation. Using nonacetylate salicylates, such as choline magnesium trisalicylate, which do not interfere with platelet function, can minimize the risk of bleeding problems.[11]

There are 3 basic mechanisms by which NSAIDs affect pain perception: inhibiting the conversion of arachidonic acid to prostaglandin G_2 by inhibiting the enzyme cyclooxygenase (COX), inhibiting the release of inflammatory mediators, and producing central effect on pain perception.[9] Two isoenzymes of prostaglandin synthetase and cyclooxygenase have been identified—COX-1 and COX-2. COX-1 is primarily responsible for gastric protection, renal vasodilation, and vascular hemostasis. It is found mainly in gastric mucosa, platelets, kidney, and vascular endothelia. COX-2, found in inflamed tissues, appears to be responsible for the regulation of inflammation. COX-2 isoenzymes are located in the brain, renal tissues, and the female reproductive tract.[3,9,12] NSAIDs have been found to cause severe adverse reactions such as gastric ulceration, bleeding because of inhibition of platelet aggregation, and renal dysfunction. The risk of ulceration is threefold in patients using NSAIDs in the general population.[13] Research began for the development of a selective COX-2 inhibitor to provide anti-inflammatory effects without such debilitating adverse effects.[3]

There have been 3 selective COX-2 inhibitors approved by the Food and Drug Administration (FDA): celecoxib (Celebrex®, Pharmacia, Peapack, NJ), rofecoxib (Vioxx®, Merck, Whitehouse

Station, NJ), and valdecoxib (Bextra®, Pharmacia). Results from the Celecoxib Long-term Arthritis Safety Study (CLASS) and the Vioxx GastroIntestinal Outcome Research (VIGOR) trial found after evaluating 8000 patients (between the 2 studies) that rofecoxib and celecoxib decrease serious GI events, including perforation, obstruction, bleeding, and ulceration by approximately 50%.[9] In the CLASS study, 400 mg of celecoxib twice a day was compared with standard doses of ibuprofen and diclofenac sodium for treatment of rheumatoid arthritis. Drug effectiveness found celecoxib to be similar to the 2 NSAIDs, ibuprofen and diclofenac sodium. The overall safety of celecoxib at twice the highest approved dose for arthritis was similar to ibuprofen and diclofenac sodium. Patients taking low-dose aspirin and celecoxib had a higher rate of upper GI events than those taking celecoxib alone.[14] COX-2 inhibitors' adverse effects are delays in ulcer healing and anaphylactic reactions in asthmatic patients who have severe bronchospasms after taking NSAIDs or aspirin.

Concerns about conclusions of thrombotic events were reported. The VIGOR trial did not permit patients to take their daily aspirin (approximately 4% of the patients), even if they were at risk for cardiovascular events, as patients did in the CLASS study. The VIGOR study resulted in approximately 0.8% of trial patients versus 0.4% of control subjects sustained a thrombotic event. The CLASS trial revealed no significant difference in cardiovascular events between patients receiving celecoxib and the control group taking diclofenac sodium. Postulations were that diclofenac has a weak antiplatelet effect compared with naproxen, which has a very potent antiplatelet effect. COX-2 inhibitors do not inhibit the production of thromboxane A_2 and, therefore, has a minimal effect, if any, on platelets. Also rofecoxib at 50 mg (used in the VIGOR trial) may cause edema in approximately 4% of patients (higher values than the control subjects) and an increase in blood pressure in 8% of patients compared with 1.3% of control subjects.[9,15] The CLASS trial results found no difference in rates of hypertension, swelling, and cardiovascular problems, such as heart attack, between patients treated with celecoxib and those treated with ibuprofen or diclofenac sodium.[14]

Opioids

Opioid receptors are located in the central nervous system (CNS) and periphery. Three primary sites for the receptors have been identified: afferent nerves, postsynaptic spinal neurons, and the central spinothalamic tract.[16]

Below are factors to consider when prescribing opioids:

- Evaluation—Evaluate the physical aspects of the patient initially and reevaluate the drug regimen regularly to obtain maximum relief and minimize adverse effects; this should be done once or twice daily.[5]

- Prevention and treatment of adverse effects—This includes constipation, nausea/vomiting, respiratory depression, etc. Tolerance to the constipating effects of opioids do not occur; therefore, regularly scheduled stool softeners such as Senekot-

S® (senna + docusate sodium 50 mg) 1-2 tablets 1 to 3 times a day are indicated.[17]

- Route of administration—In general, the oral route is preferred unless barriers, such as the patient is unable to swallow, occur. The oral route of drug administration usually has a slower onset of action and a longer duration of effect. Parenteral medications tend to have a more rapid onset of action with a shorter duration of effect. Alternatives routes to oral drug administration are parenteral, intranasal, transdermal, rectal, and sublingual.[18]

- Schedule—Give opioids on a regular schedule to prevent a loss of efficacy between doses; this will prevent recurring pain rather than having to treat breakthrough pain (BTP). BTP has been defined as a transient increase in pain intensity in conjunction with a well-controlled baseline pain. When dosing opioids for BTP, use 15% to 20% of the 24-hour dose of the regularly scheduled opioids with immediate-release products. For example, a patient receiving a total daily dose of 100 mg of extended-release morphine sulfate should also have available 15-20 mg of immediate-release morphine sulfate every 4 hours as needed for BTP. When patients need more than 3 extra doses of immediate-release opioids in 24 hours, it is time to increase the dose of the sustained-release opioid by 25%-50%. Oral doses are equal to 3 times the intramuscular, intravenous push, and subcutaneous dose (of which the latter is a 1:1:1 ratio).[1,18]

- Special patients—Beware of adjustments that need to be made on the dose, drug, interval, and route when giving opioids to children, elderly (more sensitive to the analgesic effects of opioids, and duration of action is longer in these patients), cognitively and physically impaired, and known or suspected abusers (who need higher starting doses and shorter dosing intervals).

- Titration—When titrating, decrease or increase the dose by 25% of the previous dose every 24 to 48 hours. In severe cases, clonidine given short term in titrated doses will usually control serious autonomic signs. The physiologic effects of opioid withdrawal are usually not life threatening as seen in alcohol withdrawal.[19]

The opioids that are commercially available can act at 5 known major receptors (Table 1). These receptors are named mu (μ), kappa (κ), sigma (σ), delta (δ), and epsilon (ε). Some receptors have subtypes and specific actions when activated.[20]

Table 1. Major Receptors and Mediations of Opioids

Receptors	Mediation
Mu (μ_1 and μ_2)	Euphoria, miosis, morphine-like supraspinal analgesia, reduced GI motility, physical and respiratory depression
Kappa (κ_1, κ_2, κ_3)	Miosis, pentazocine-like spinal analgesia, sedation
Sigma (σ)	Dysphoria, psychotomimetic actions (hallucinations), respiratory and vasomotor stimulation caused by drugs with opioid antagonistic activity
Delta (δ) and Epsilon (ε)	Generally bind enkephalins and endorphins respectively

Opioids affect various organ systems. Listed below are multiple side effects that may occur with opioid use.[18]

Dermatologic
Opioids can cause flushing, pruritis, and red eyes mainly attributable to histamine release.

Central Nervous System
Opioids can cause alterations in mood, apathy, decreased body temperature, drowsiness, dysphoria, euphoria, hallucinations, mental confusion, and relaxation. Elderly patients are particularly susceptible to the CNS depressant effects of opioids.

Cardiovascular
Opioids can cause fainting, inhibition of baroreceptors, orthostatic hypotension, and peripheral vasodilation.

Gastrointestinal
Stomach: By direct stimulation of the chemoreceptor trigger zone (CTZ) in the medulla, opioids cause nausea and vomiting. Opioids can also decrease gastric motility, which results in prolonging gastric emptying that can lead to esophageal reflux.

Biliary Tract: Opioids increase the tone of smooth muscle in the Sphincter of Oddi, causing constriction, leading to epigastric pain or biliary colic.

Small intestine: Opioids decrease biliary, intestinal, and pancreatic secretions, which delay the digestion of food. Periodic spasms may occur because of an increase in resting tone.

Large intestine: Opioids can cause constipation by decreasing propulsive peristaltic waves in the colon and increasing smooth muscle tone until it spasms. Elderly patients are particularly susceptible to the constipating effects of opioids.

Respiratory
Opioids depress the number of respirations by reducing the sensitivity of the respiratory center to carbon dioxide and diminishing tidal volume. By directly affecting the cough center in the medulla, opioids suppress the cough reflex.

Genitourinary
Opioids can cause difficulty with urination (dysuria) and urinary urgency because they can increase smooth muscle tone of the urinary tract and cause spasms of the ureters.

The following opioids—morphine, fentanyl, methadone, hydromorphone, oxycodone, hydrocodone, and meperidine—are indicated for the treatment of pain.[3]

Morphine (Roxanol®, Roxanol SR®, MS Contin®, MSIR®, Kadian®, RMS® [rectal], Oramorph SR®)

Morphine is the most commonly used opioid to control severe pain because of its wide availability, varied formulations, comparatively low cost, efficacy, no "ceiling effect," and no direct organ damage even after long-term use.

Morphine is metabolized in the liver to morphine-3-glucuronide and morphine-6-glucuronide. Morphine-3-glucuronide lacks analgesic properties or respiratory depressant effects but can cause anxiety, myoclonus, and nightmares. Morphine-6-glucuronide (M6G) is a hydrophilic metabolite that is 10-60 times as potent as morphine. M6G and morphine possess analgesic actions and are responsible for adverse effects such as confusion, constipation, delirium, drowsiness, hallucinations, and miosis. After morphine is metabolized, the kidney eliminates the metabolites.[21]

For dosing morphine, always start with an immediate-release form and titrate to effect. Once a stabilized dose and interval are found to constantly relieve pain adequately and minimize adverse effects, then a sustained-release form can then be used in place of the immediate-release form.

When changing routes of administration in chronically treated patients, be aware that oral doses are about one-third as effective as parenteral doses. (300 mg oral morphine = 100 mg IV, IM, SC = 10 mg epidural = 1 mg intrathecal). The half-life of morphine in adults is 1.5-4 hours and 4.5-13.3 hours in neonates.

For patients with cirrhosis, excessive sedation may occur with any of the below dosage regimens. In renal impairment, give 25% less of the dose if creatinine clearance is 10-50 ml/min, give 50% of the dose if the creatinine clearance is <10 ml/min. Do not use morphine for patients who have allergies to sulfites, biliary tract surgery, and severe respiratory depression. Use caution for patients with asthma, increased intracranial pressure, emphysema, epilepsy, hypotension, and kidney and liver impairment.[22]

Table 2 below contains various routes and dosages of morphine:[23]

Table 2. Routes and Dosages of Morphine

Route	Dose for Children	Dose for Adults	Special Considerations
Continuous IV infusion	Cancer/sickle cell pain: 0.0252 mg/kg/h Postoperative pain: 0.01-0.04 mg/kg/h	0.1-1 mg/ml in D_5W by controlled infusion	Higher concentrations have been used in adults.
Continuous SC	Same dose as above	0.8-10 mg/h, up to	

infusion		80 mg/h	
Epidural		Continuous infusion 0.083-0.166 mg/h An intermittent additional injection of 1-2 mg can be given if analgesia is not initially relieved; no more than 10 mg/24h	Aged or debilitated patients: Doses of <5 mg should provide adequate analgesia for up to 24 hours; however, give with extreme caution.
Intermittent IV infusion	Analgesia/sedation: 0.05-0.1 mg/kg 5 minutes before the procedure	*See paragraph below	For adolescents >12 years for analgesia/sedation: give 3-4 mg IV and repeat in 5 minutes if needed.
Intramuscular and Subcutaneous	0.05-0.1-0.2 mg/kg every 2-4 hours, no more than 15 mg per dose	2.5-20 mg 70 kg body weight (10 mg average) every 2-4-6 hours	
Intrathecal		0.2-1 mg in the lumbar area as a single injection can provide satisfactory analgesia for 24 hours.	Do not give repeated intrathecal doses. Use another route of administration. Intrathecal use is associated with a higher incidence of respiratory depression than with epidural use.
Intravenous	See Continuous and/or Intermittent IV infusion		
Oral (oral solutions can also be given sublingually)	Immediate release: 0.2-0.5 mg/kg/dose every 4-6 hours as needed. Sustained release: 0.3-0.6 mg/kg/dose every 12 hours routine (not as needed)	Immediate release: 10-30 mg every 4 hours as needed Sustained release: 15-30 mg every 8-12 hours routinely (not on an as-needed basis)	

Rectal		5-30 mg every 4 hours routine (10-20 mg average)	An unlabeled use for sustained-release morphine sulfate tablets is to place them in a gelatin capsule and use them as a suppository; dosing and interval same as sustained-release oral dosing.
Small Volume Nebulizer (SVN)		10 mg every 4 hours for COPD or dyspnea associated with left ventricular failure and pulmonary edema[24]	ADR: Bronchospasm caused by histamine release. - Use preservative-free normal saline solution. - Give 1st dose in presence of licensed health care professional.

*Intermittent IV infusion in Adults: Give over 4-5 minutes in 4-5 mls of sterile water for injection, a dose range of 2-15 mg/70 kg of body weight is used (8-15 mg for MI patients). Smaller doses of this range can be repeated every 3-4 hours.

The kinetics of morphine are dependent upon the dosage form used. Morphine peaks and duration of action are listed below in Table 3.

Table 3. Routes, Peaks, and Duration of Action of Morphine

Route	Peak	Duration
Immediate release tablets	60 minutes	4-5 hours
Sustained release tablets	60 minutes	8-12 hours
Oral solution	60 minutes	4-5 hours
IM injection	30-60 minutes	4-5 hours
Subcutaneous injections	50-90 minutes	4-5 hours
IV injection	20 minutes	4-5 hours
Suppositories	20-60 minutes	3-7 hours

Table 4. Equianalgesic Doses of Various Opioids[25]

Drug	Equianalgesic Dose (mg)		Peak (hours)	Duration (hours)
	I.M.	P.O.		
Fentanyl	0.1	NA	NDA	1 to 2
Hydromorphone	1.5	7.5	0.5 to 1	4 to 5
Meperidine	75	300	0.5 to 1	2 to 4
Methadone	10	20	0.5 to 1	4 to 6
Morphine	10	30	0.5 to 1	3 to 7
Oxycodone	NA	15	1	4 to 6

NA: Not applicable; NDA: No data available

Fentanyl (Actiq®, Duragesic®, Sublimaze®)

As the second most potent opioid on the U.S. market, fentanyl injection is used preoperatively, perioperatively, and postoperatively by the IM or IV route as an analgesic. Fentanyl injection is also used IV for the induction of anesthesia. It is used with other general anesthetics in cardiovascular, neurologic, and orthopedic surgery for high-risk patients. Giving 10 mcg of fentanyl IV is equivalent to using 1 mg of morphine IV. When the injection is used in adults for pain, the dose range is 50-100 mcg (IM or IV), and can be repeated in 1-2 hours. For children, a continuous infusion is used at a range of 1-3 mcg/kg/h. Fentanyl injection is also used in epidural infusions (usually with 0.0625%-0.125% preservative-free bupivacaine added) and PCA pumps (5-10 mcg/ml concentrations).

The fentanyl lozenge (Actiq®) on a stick, also referred as oral transmucosal fentanyl citrate (OTFC), is labeled only for breakthrough cancer pain with patients who are already receiving and are tolerant to opioid therapy (patients taking >60 mg morphine per day, 50 mcg/h transdermal fentanyl or equianalgesic doses of alternative opioids for >1 week). Do not use OTFC for opioid-tolerant children <16 years of age. There is no correlation between the dose of Duragesic® patch and the dose of OTFC. Dosing guidelines for OTFC were established from controlled studies of patients experiencing cancer-related, breakthrough pain.[26,27] Over a period of days, patients titrated their dose from 200 mcg until the pain was relieved or after receiving 4 lozenges, whichever came first. The trials concluded that approximately 75% of the patients acquired a safe and effective dose of OTFC. Most common side effects were nausea, dizziness, somnolence, vomiting, constipation, and headache.

Special Considerations for Oral Transmucosal Fentanyl Citrate

OTFC is positioned in the patient's mouth between the check and lower gum. The patient should suck (not chew) the lozenge and move it from one side of the mouth to the other by use of the attached handle, consuming the lozenge over a 15-minute period. The initial dose of OTFC is 200 mcg with an additional dose that can be given 30 minutes after the start of the prior dose (15 minutes after finishing the prior dose) for each breakthrough episode. Six doses of a single strength are to be

used before advancing to a higher dose. Once an adequate dose is established (when a typical breakthrough episode is treated with a single unit), the number of doses per day should not exceed 4 units. Approximately 50% the dose of OTFC is available systemically: 25% is rapidly absorbed from the buccal mucosa, and the GI tract absorbs 25%.[22]

Fentanyl Transdermal System (Duragesic®)

Duragesic® patch is labeled for treatment of chronic pain for patients requiring constant opioid analgesia for pain that can't be managed by NSAIDs, NSAID/opioid combinations, or as-needed dosing of short-acting opioids. Most patients are adequately controlled with a Duragesic® dose every 72 hours; however, some patients may require a new patch every 48 hours. Duragesic® patch onset of action is approximately12 hours. It may take up to 72 hours to achieve the full effect and at least 17 hours for serum levels to decrease by 50%.

Fentanyl Transdermal System (Duragesic®) should **not** be used for the following reasons:

- In the treatment of acute pain, postoperative pain, intermittent pain, or mild pain responsive to nonopioids, or as-needed therapy
- In initial doses exceeding 25 mcg/h (unless the patient has preexisting opioid tolerance)
- In children <12 years or patients <18 years who weigh <50 kg

Special Considerations for the Fentanyl Transdermal System (Duragesic®)

After determining the dose (patches should not be cut in fractional pieces), an application site must be selected. Try to select a site surface that is flat, nonirradiated, and contains some subcutaneous fat, such as an area of the back, chest, flank, or upper arm.[23] Cachectic patients have erratic absorption with Duragesic® patches because they lack sufficient subcutaneous fat stores. Make sure the patient has a normal body temperature (no fever) and the environmental exposure to heat such as electric blankets, heating pads, heated car seats, and heated waterbeds are limited, as this accelerates release of fentanyl from the patch, which can result in sudden excessive levels.

Methadone (Dolophine®)

Methadone may also be considered for the relief of severe cancer pain, but is not recommended for initial therapy because of its long half-life and risk of drug accumulation. It is absorbed well orally and is less expensive than hydromorphone. Its effect on cough, bowel motility, and biliary tone are similar to those of morphine. It is highly protein bound, and repeated dosing leads to a gradual accumulation in the tissues. After the drug is discontinued, the withdrawal is relatively mild but prolonged. The usual adult dosage is oral; IM; or SC 2.5 mg to 10 mg every 3 to 8 hours as needed, up to 5-20 mg every 6-8 hours. Repeated doses and dosage may need to be adjusted downward after 3-5 days to prevent toxic effects. Some patients may benefit from every 8- to 12-hour dosing interval. Administer 50%-75% of the normal dose in renal impairment (CrCl<10 ml/min). Compared with morphine, methadone does not have active metabolites and morphine does. Methadone has an elimination half-life of 30 hours,

whereas morphine has only a half-life of 3-4 hours. Methadone has an oral bioavailability of 80% and morphine is only 35%. These pharmacokinetic differences are what make methadone more difficult to adjust the doses than with morphine.[28]

Hydromorphone (Dilaudid®, Dilaudid-5®, Dilaudid-HP®)

Hydromorphone's main advantage over morphine is its potency that allows for smaller injections or infusion volumes in patients who require opioid parenteral administration. Hydromorphone potency to morphine is 4:1 up to 8:1 (5:1 on average) orally and 7:1 parenterally (1.5 mg IM hydromorphone = 10 mg IM morphine).[29] Studies suggest that hydromorphone has the same efficacy and adverse effects as morphine.[30] The adult dose for moderate pain starts orally with 2 to 4 mg every 4 to 6 hours for pain. The adult parenteral dose is 1 to 2 mg SC or IM every 4 to 6 hours as needed, and for severe pain administer 3 to 4 mg every 4 to 6 hours as needed.[23]

Oxycodone (Endocodone®, M-Oxy®, OxyContin®, Oxydose®, OxyFAST®, OxyIR®, Percolone®, and Roxicodone®)

Oxycodone is an oral opioid analgesic and is available in many different dosage forms with acetaminophen or aspirin but not by injection or transdermal. Oral oxycodone is approximately 1.5 times stronger than oral morphine. Its advantage in renal failure, like hydromorphone, is the lack of detectable, clinically relevant active metabolites, therefore avoiding accumulation with its toxic reactions.[29] The sustained-release tablets may be placed in gelatin capsules and used rectally.

Hydrocodone (Lortab®, Lorcet®, Vicodin®, Vicoprofen®)

Hydrocodone is not yet available as a single entity itself, but is used in combination products with mainly acetaminophen but also aspirin and even ibuprofen. It is available with chlorpheniramine in a sustained-release suspension as Tussionex® but not in tablet form. Use caution in dosing hydrocodone combination products and do not exceed the recommended 4 to 6 gm of acetaminophen, which can cause hepatotoxicity; or in patients contraindicated for aspirin use. The various antitussive combinations with hydrocodone will not be discussed here. There are many different strength combinations of hydrocodone and acetaminophen, too numerous to list. Vicodin®, hydrocodone/acetaminophen 5/500mg, which is prescribed as needed for moderate-to-severe pain, is dosed at 1-2 tablets every 4-6 hours.[23]

Meperidine (Demerol®)

Meperidine was developed during World War II (as was methadone) for an anticholinergic drug because it was chemically related to atropine, but it was found to have considerable analgesic properties.[31] In addition to its analgesic action, meperidine is used as an adjunct to anesthesia and in preoperative sedation. The dose for pain relief in adults is 50 to 150 mg IM, SC, or orally every 3 to 4 hours as needed.[23] Meperidine is not recommended for cancer patients who need continued opioid therapy for pain control because accumulation of its metabolite, normeperidine, may lead to dysphoria, agitation, and seizures.[32] Normeperidine has a half-life of 15 to 40 hours, whereas meperidine has a half-life of only 3 hours. The activity of normeperidine

cannot be reversed by naloxone. Compared with morphine, meperidine causes more hypotension, more histamine release, but is better absorbed by the GI tract. Meperidine is associated with less constipation, urinary retention, and biliary tract spasm than morphine. Meperidine increases heart rate and myocardial contractility, which is unique compared with other opioids. Meperidine is not to be used for any patient currently taking or who has taken any monoamine oxidase (MAO) inhibitors within the past 2 weeks, as this interaction could result in a fatal hypertensive crisis.[33]

NONOPIOIDS

Tramadol (Ultram®, Ultracet®)

Tramadol is a centrally acting analgesic that weakly binds to μ-opioid receptors and inhibits the reuptake of norepinephrine and serotonin. The analgesic efficacy of 50 mg of tramadol is equivalent to 60 mg of codeine or 30 mg codeine plus 650 mg of acetaminophen. Common side effects include nausea, dizziness, constipation, sedation, and headache. Patients with cancer who are most likely to benefit from tramadol are those with mild-to-moderate pain. Since tramadol inhibits the reuptake of serotonin and norepinephrine this may make tramadol a good alternative to tricyclic antidepressants owing to a similar mechanism of action without the anticholinergic side effects.[34]

NEUROPATHIC PAIN DRUGS

Adjuvant therapy refers to a drug that has a primary indication other than pain, but is analgesic in certain circumstances. Bone metastasis, visceral distension, and nerve compression are all disease states that may require other alternatives or additions to opioid therapy. Medications commonly used as adjuvant treatment for chronic pain include tricyclic antidepressants, anticonvulsants, corticosteroids, and antiarrhythmics.[11]

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are thought to relieve pain by inhibiting serotonin and norepinephrine or possibly by blocking sodium channels. Studies have demonstrated that mixed serotonin and norepinephrine reuptake inhibitors are more effective than selective serotonin reuptake inhibitors (SSRIs). Paroxetine (Paxil®), a SSRI, surprisingly has been documented in providing some analgesic effect with fewer side effects than TCAs.[35-37] Amitriptyline has been the most widely studied and has documented efficacy of all the TCAs.[37] Nevertheless, the side effect profile of TCAs makes them difficult to tolerate. TCA anticholinergic side effects such as sedation, weight gain, orthostatic hypotension, dry mouth, constipation, and urinary retention are commonly experienced in patients. Amitriptyline starting doses should begin at 25 mg at bedtime (10 mg in the elderly) and increase every 2 to 3 days to a maintenance dose of 50 to 150 mg at bedtime. Other TCAs used are nortriptyline, with maintenance dosages of 100 to 150 mg, and desipramine 50 to 200 mg at bedtime. Pain relief usually takes 2 to 4 weeks after therapy is initiated.[5] Use with caution in patients with epilepsy because TCAs lower the seizure threshold at high doses. (Maximum dose of amitriptyline is 300 mg/day). TCAs also cause tachycardia and prolong the PR and QRS intervals by direct membrane stabilization.[3]

Table 5 lists multiple TCAs and their corresponding maintenance doses, which have unlabeled uses as analgesic adjuncts for phantom limb pain and chronic pain (migraine, chronic tension headache, diabetic neuropathy, tic douloureux, cancer pain, peripheral neuropathy with pain, postherpetic neuralgia, and arthritic pain).[23]

Table 5. Maintenance Doses for Tricyclic Antidepressants

Medication	Maintenance Doses
Amitriptyline (Elavil®)	75 to 300 mg/day
Doxepin (Sinequan®)	30 to 300 mg/day
Imipramine (Tofranil®)	75 to 300 mg/day
Nortriptyline (Pamelor®)	50 to 150 mg/day
Desipramine (Norpramin®)	75 to 300 mg/day
Amoxapine (Ascendin®)	100 to 300mg/day
Protriptyline (Vivactil®)	15 to 60 mg/day

Carbamazepine (Tegretol®)

Carbamazepine is the only medication with a FDA-approved indication for the pain associated with trigeminal neuralgia. Trigeminal neuralgia, also known as tic douloureux, is a sharp, often electric shock–like pain that occurs in a rapid series of jolts (lasting seconds to minutes) in one or more divisions of the trigeminal nerve. Carbamazepine commonly causes sedation, dizziness, nausea, and unsteadiness; these effects can be minimized by low initial doses (100 mg twice a day) and gradual titration (maximum typical daily doses are 600 mg to 1000 mg). Important side effects include bone marrow suppression, particularly during early treatment. Therefore, complete blood count (CBC) measurements are suggested at baseline, every 2 to 4 weeks for 3 months, then every 6 to 12 months. Skin rashes, liver function abnormalities, and hyponatremia have also been reported. Carbamazepine is a heteroinducer; it induces its own metabolism, as well as the metabolism of other drugs. Carbamazepine has numerous drug interactions such as decreasing the effects of warfarin, cyclosporine, doxycycline, oral contraceptives, phenytoin, theophylline, benzodiazepines, ethosuximide, valproic acid, corticosteroids, and thyroid hormones. The following medications may increase carbamazepine serum concentrations and cause toxicity, erythromycin, isoniazid, propoxyphene, verapamil, danazol, diltiazem, and cimetidine.[3,5,22]

Gabapentin (Neurontin®)

Gabapentin has demonstrated efficacy in randomized, controlled clinical trials for significant pain relief and sleep disturbances in diabetic neuropathy and postherpetic neuralgia.[38] Diabetic neuropathy is a heterogeneous disorder found in diabetic patients that encompasses a wide range of abnormalities affecting proximal and distal peripheral sensory and motor nerves, as well as the autonomic nervous system. Postherpetic neuralgia is a syndrome of often intractable, neuropathic pain following herpes zoster, which escapes effective treatment in many patients.[39] Dosages are titrated

from 900 to 3600 mg per day or maximum tolerated dosage. There is no required monitoring of CBCs, liver function tests (LFTs), or serum levels with gabapentin. The most common adverse effects are dizziness, somnolence, weight gain, peripheral edema, and confusion. First-line use of gabapentin might be considered for patients with contraindications to TCAs (long QT syndrome or significant conduction system disease, recent myocardial infarction [MI], unstable angina, congestive failure, frequent premature ventricular contractions, or sustained ventricular arrhythmias), and patients with orthostatic hypotension.[40]

CORTICOSTEROIDS

Corticosteroids, such as dexamethasone, prednisone, and methylprednisolone, are highly effective for relief of pain associated with spinal cord compression, increased intracranial pressure, superior vena cava syndrome, metastatic bone pain, neuropathic pain caused by infiltration or compression by tumor, and hepatic capsular distension. They also have added benefits in chronic pain patients, especially cancer patients, in increasing appetite, mood, and decreasing nausea.[5] Bone pain typically cannot be completely controlled with only narcotics. Therefore, adjuvant agents are added to the narcotic regimen. First-line adjuvant therapies for bone pain include NSAIDs and corticosteroids such as prednisone (30 to 60 mg per day taken orally), dexamethasone (Decadron®; 16 mg per day taken orally), and methylprednisolone (Medrol®; 120 mg per day taken orally).[41]

KETAMINE (Ketalar®)

Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist that selectively interrupts association pathways in the brain before causing sensory blockade by preferentially depressing the cortex, limbic system, and reticular activation system. Ketamine produces an anesthetic state called "dissociative anesthesia." The patient appears to be awake but is unconscious ("doll eyes"), immobile, and does not respond to pain. Ketamine is dosed as IM 3-10 mg/kg, IV 0.5-4.5 mg/kg, or continuous infusion 0.1-0.5 mg/min. Amnesia may persist for 1-2 hours for IM and 3-4 hours for IV.[42] A subanesthetic dose of ketamine has analgesic properties. The dose for analgesia is between 1/10 and 1/5 of the anesthetic dose. The most common side effects of ketamine in subanesthetic doses are altered body image perception, modulation in hearing, visual disturbances, dizziness, anxiety, aggression, a feeling of illness, and nausea. The incidence of psychic disturbances varies from less than 5% up to 30%.[43]

DEXTROMETHORPHAN

Dextromethorphan is also a NMDA receptor antagonist used as a cough suppressant. It has a good safety profile with no serious adverse effects. There is conflicting evidence in its efficacy in the treatment of neuropathic pain. The reason for this may be the variation in dextromethorphan doses and duration of treatment between the studies. In a randomized control study, at 90 mg/day dextromethorphan did not have any significant analgesic effect when used in addition to conventional treatment with an NSAID, dextropropoxyphene, or morphine.[43] However, controlled trials

found that dextromethorphan does potentiate the analgesic effects of morphine.[44] Nelson et al. reported that high doses of oral dextromethorphan administration up to 380 mg/day for 6 weeks reduced the intensity of pain in patients with painful diabetic peripheral neuropathy. Seven out of 13 patients reported moderate or greater relief of pain during dextromethorphan treatment compared with none with placebo. [45]

MEXILETINE (Mexitil®)

Mexiletine is an antiarrhythmic agent related to the local anesthetic lidocaine. Both lidocaine and mexiletine act as sodium channel antagonists, reducing discharges in damaged peripheral nerves responsible for pain generation. Mexiletine has been well described for alleviating neuropathic pain attributable to phantom limb pain, traumatic nerve injury, HIV-related neuropathy, postherpetic neuralgia, trigeminal neuralgia, alcoholism-related painful neuropathy, and diabetic neuropathy. The dose is 150 mg to 200 mg once or twice a day. The dose should be titrated, increasing by 1 tablet every 5 to 7 days until either pain relief, intolerable side effects, or a toxic serum level (>2 μg/ml) are reached. Common side effects include nausea, heartburn, dizziness, tremor, nervousness, and headache.[42]

SUMMARY

Since pharmacists are the most accessible health care professional, they are the ones who have the best opportunity to greatly impact a patient's quality of life. Millions of people are plagued with chronic pain. Health care professionals are more accountable than ever before in improving patient outcomes. Specialized knowledge of various pain syndromes, pharmacokinetics, drug interactions, and treatment options are essential in providing effective pain management. With pharmacologic interventions and a multidisciplinary approach, relief from chronic pain can be achieved.

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