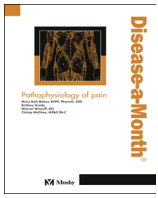
Disease-a-Month 59 (2013) 330–358

Contents lists available at ScienceDirect

Disease-a-Month

journal homepage: www.elsevier.com/locate/disamonth



Pathophysiology of pain

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1. Pathophysiology of pain

1.1. Overview of pain pathways

Pain occurring at the end of life is often a complex amalgam of symptoms that arise from neuropathic, somatic, and visceral pain syndromes. Likewise, the stimuli from which the pain syndromes originate are complex and may include inflammatory, neuropathic, and ischemic components.[1] The palliative management of pain is further complicated by nociceptor sensitization that often occurs in chronic pain syndromes[1–3] and by the affective components involved. Although neural plasticity and sensitization obfuscate the direct etiologies of chronic pain, it is ultimately pain signal transduction that underlies chronic pain; thus an understanding of acute pain signaling pathways is critical in the provision of effective palliative pain management.

Pain itself, like joy or pleasure, initiates from within. It is the end result of central processing of sensory stimuli. Sensations of acute pain occur when stimuli of sufficient intensity lead to the depolarization of high-threshold nociceptors. Impulses generated from exposure to heat, chemical injury, and mechanical stimuli are transduced into electrical signals that are carried to the dorsal horn of the spinal cord, where the primary neurons form synapses with secondary neurons that ascend to the central nervous system (CNS). Lightly myelinated Aδ fibers rapidly carry signals that relay and pinpoint the topographic origins of sharp pain, while unmyelinated C-fibers more slowly carry diffuse signals that relay burning or dull aching sensations. Normally, large myelinated Aα and Aβ very rapidly conduct non-noxious signals (e.g., vibration and touch); signaling through these fibers may become deranged during inflammation or after healing of traumatic tissues, leading to aberrant pain sensations.[4]

In the dorsal horn, the primary neurons synapse with secondary neurons and interneurons located in different layers of the dorsal horn. Secondary neurons with cell bodies that originate in Rexed layer I and II are specific for noxious stimulation of mechanical and thermal origin; these are the neurons that comprise the neospinothalamic tract, which transmits topographic and intensity-related information to the cortex for rapid response. Secondary neurons whose cell bodies lie in Rexed area V are known as non-specific, convergent, polymodal, or wide-dynamic-range neurons because they can be activated both by fibers that carry painful stimuli of tactile, muscular, or visceral origin and by fibers that carry non-noxious stimuli. These secondary

0011-5029/$ - see front matter © 2013 Published by Mosby, Inc.
http://dx.doi.org/10.1016/j.disamonth.2013.05.003

neurons form the paleospinothalamic tract, which carries non-intensity-related and topographically vague information to the reticular formation, pons, limbic system, and mid brain. The affective aversive qualities of pain are perceived after processing of signals received via the paleospinothalamic tract.

The ascending input is multiply interconnected with areas of the brain responsible for memory and with areas that modulate the dorsal horn via descending pathways. The relaying and processing of pain signals relies on a complex network of redundant and dynamic systems that can modulate both transmission and perception of the pain signal. Pain signaling pathways may become dysfunctional, leading to perception of pain in the absence of tissue damage. Inflammation and/or trauma of peripheral tissues and nerves may lead to this dysfunctional signaling, also known as pathologic pain. Lesions in the central and peripheral nervous systems may lead to neuropathic pain.[4]

The molecular mechanisms involved in signal transduction and signal modulation are often the target of pharmacologic interventions for acute, pathologic, and neuropathic pain syndromes. Several of these signal modulation and transduction pathways are well-characterized. Pharmacologic agents used in pain management often act to enhance inhibitory signals or to block excitatory signals.

1.2. Pain signal transduction

1.2.1. Excitation of primary afferent neurons

Specific protein molecules or receptors located in the peripheral terminals of primary nociceptive neurons serve to detect and initiate a signal intended to alert the organism regarding potential or actual tissue damage. When these receptors encounter the appropriate specific stimulus (e.g., high heat, extreme cold, chemicals, or excessive pressure) that is of sufficient intensity, the receptor molecule undergoes a conformational change that transduces the noxious signal into an electrical current by triggering the opening of depolarizing cationic ion channels or the closing of outward potassium channels.[2]

Polymodal afferent sensory neurons respond to thermal, mechanical, and/or chemical stimuli, while other afferent sensory neurons are modality-selective.[2] Some receptors act to instigate a signal, while others act to sensitize the peripheral terminal to instigating signals.[5] In addition to transducing nociceptive signals from the periphery to the CNS, some afferent nerves release substances from their peripheral terminals either to mediate normal tissue integrity in the absence of injury (e.g., bone remodeling) or to contribute to the inflammatory cascade (e.g., edema caused by substance P) in a positive feedback loop.[2]

Several of the molecules that transduce specific types of signals have been identified to date.[1–5] Members of the transient receptor potential (TRP) cation channel family are responsible for detection and transduction of both thermal and chemical signals. Some members of the TRP family are activated at low temperatures, while other receptors respond to heat, drops in local pH, or chemical ligands such as capsaicin (the vanilloid constituent that provides the “hot” in hot peppers). Acid-sensitive ion channels (ASIC) are activated by increases in hydrogen ion concentration that often result from ischemia and inflammation. Excesses of ATP that occur secondary to cell rupture signal to purinergic receptors; the P2X is a purine-activated ligand-operated ion channel,[6] while the P2Y receptor is a g-protein-coupled receptor.[5] Still other receptors are stimulated by kinin peptides formed when serine protease kallikreins activate kininogens during tissue inflammation and damage. Expression of the bradykinin 1 (B1) receptor is induced by bacterial lipopolysaccharide and inflammatory cytokines, while the bradykinin 2 receptor (B2) is constitutively expressed. Both of these bradykinin receptors are coupled to Gq proteins; stimulation leads to formation of inositol 1.4.5-triphosphate and diacylglycerol with subsequent increases in intracellular calcium levels. Prostaglandin E2 and prostacyclin are downstream products that form subsequent to B2 receptor activation,[5] further amplifying the nociceptive signal.[3] Several of these signaling molecules have been proposed as potential targets for pain management.[7–9]

Table 1
Compiled from Refs. 5,9, and 13

Ion channel	Function	Drugs that modify function
Calcium	Inward channel, primary driver for most intracellular responses to stimulation	Pregabalin Gabapentin Ziconotide
Sodium	Inward channel; influx of sodium through open channels makes membrane potential less negative, bringing it closer to the threshold potential necessary to initiate an action potential	Local anesthetics Carbamazepine Phenytoin
Chloride	Inward channel; influx of chloride makes the membrane potential more negative (hyperpolarized)	Benzodiazepines[a] (amplify $GABA_A$ induced opening of channel)
Potassium	Outward channel; efflux of potassium makes the membrane potential more negative (hyperpolarized)	Baclofen[b] Clonidine[b] Opioids[b]

[a] Benzodiazepines bind to the gamma-aminobutyric acid (GABA) type A receptor and increase the probability that GABA will cause the inward chloride ion channel to open.
[b] These agents do not directly interact with the ion channel, but rather initiate a cascade of events that ultimately increases the number of outward K^+ channels in the open state.

If the initial signal reaches the threshold or activation potential, further conduction of the signal requires the generation of an action potential via opening of depolarizing voltage-gated calcium and sodium channels or closure of hyperpolarizing potassium channels.[1,2] Six types of voltage-gated sodium channels have been identified to date on primary afferent neurons. It is of interest to note that mutations of NaV1.7 lead to significant alterations in pain, with gain of function associated with erythromelalgia and loss of function mutations resulting in congenital insensitivity to pain.[2,5] Endogenous and exogenous substances that modulate the function of these ion channels can amplify or dampen transmission of the pain signal. Local anesthetics and anti-epileptics block these voltage-gated sodium channels in a state-dependant fashion by selectively blocking sodium channels in the open state, but their utility in pain management is limited by their toxicity profiles. Table 1 summarizes these voltage-gated ion channels.

1.2.2. Dorsal root ganglion, dorsal horn, and modulation of secondary neurons

The cell bodies of the primary neurons lie within the dorsal root ganglia. During chronic and pathologic pain syndromes, the cell bodies may alter receptor expression and neurotransmitter production.[1] This variable nature of afferent pathways adds a layer of complexity to palliative pain management.

As previously mentioned, the primary afferent neurons form synapses with interneurons and secondary neurons in the dorsal horn. When an excitatory action potential reaches the terminal end of the presynaptic afferent neuron, N-type voltage-gated calcium channels open. The influx of calcium leads to vesicle docking and exocytosis of the specific neurotransmitter contained within the vesicle. The neurotransmitter molecules diffuse across the synaptic cleft to convey the signal to the secondary neuron. The released neurotransmitter may interact with its specific receptor to evoke either excitatory or inhibitory responses. Glutamate is a primary excitatory neurotransmitter; it interacts with one of three receptor subtypes: ionotropic AMPA [2-amino-3 (3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid], ionotropic NDMA (N-nitrosodimethyl-amine) receptor subtypes or g-protein-coupled mGlu receptors. Substance P is another common excitatory mediator; it interacts with the G-protein-coupled NK1 (neurokinin 1) receptor to produce a slightly slower response compared to ion channel-coupled signals. Gamma-aminobutyric acid (GABA) is a common inhibitory signaling transmitter; it may interact with either its G-protein-coupled $GABA_B$ receptor or its ionotropic $GABA_A$ receptors. Likewise, endorphins interact with Gi-protein-coupled mu and delta opioid receptors to reduce the activity of pain signaling pathways.[1,5] There is a significant amount of “cross-talk” between the signaling pathways that serve to modulate pain perception. For example, stimulation of the

NMDA receptor subtype results in positive feedback by stimulating increased expression of the AMPA receptor subtype.[2] Additionally, a rapid reflex arc connects the dorsal and ventral horns to allow for unconscious withdrawal from the painful stimulus.[1]

The C-fiber primary afferent fibers evoke both fast and slow responses in the secondary postsynaptic fibers. Activation of ionotropic receptors (e.g., AMPA and NDMA) mediates rapid transmission, while activation of metabotropic receptors (e.g., NK1) evokes a slower modulatory response. The multiplicity of pathways is thought to contribute to use-dependant functional plasticity of pain signaling.[5] Neuropeptide pathways fire primarily in response to signals of higher intensity, thus playing a pivotal role in signal modulation.

1.2.3. Modulation by descending tracts

The ascending neospinothalamic and paleospinothalamic tracts interface with higher somatosensory, memory, and efferent areas of the CNS; the efferent neurons that descend from the CNS further modulate pain signaling in the dorsal horn. Release of excitatory neurotransmitters including glutamate, substance P, and calcitonin gene-related peptide (CGRP) is thought to modulate plasticity that increases sensitivity to incoming pain signals. The increased sensitivity may be mediated by both functional plasticity (e.g., decreased signal intensity required to evoke conformational changes in receptor proteins) and by structural plasticity (e.g., up-regulation of excitatory neurotransmitter receptors, as in the aforementioned NMDA-provoked increase in AMPA receptor activation).[3]

Conversely, release of inhibitory neurotransmitters such as GABA, endogenous opiate agonist peptides (endorphins and enkephalins), norepinephrine, and serotonin acting at some serotonin receptors reduces sensitivity of secondary neurons to incoming signals by reducing calcium influx into presynaptic nerve terminals or by evoking hyperpolarization in the postsynaptic nerve terminals. Many pharmacologic interventions target these inhibitory descending pathways.

Figure and Table 2 summarize these endogenous signals and provide examples of drugs that target them.

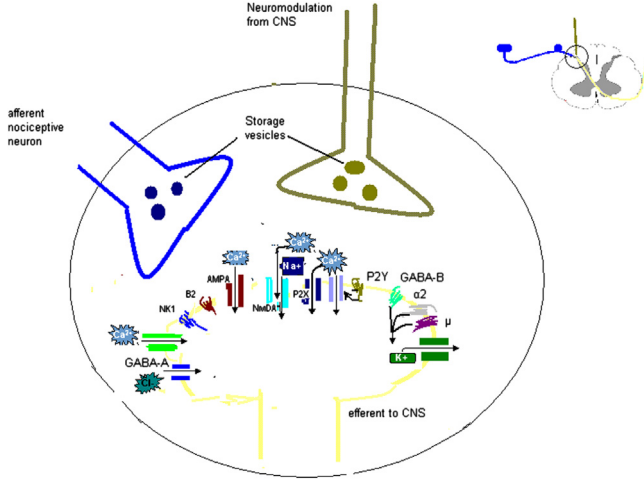

Figure. Schematic representation of synapses in dorsal horn. Dark blue represents afferent nociceptive neuron (Aδ or C fiber). Yellow represents an efferent traveling via spinothalamic tracts to CNS. Olive represents neuromodulatory fiber from CNS. Some neurotransmitters open depolarizing sodium and calcium channels to send pain signal to the CNS: glutamate on NMDA and AMPA receptors and ATP on P2X receptors. Metabotropic receptors may indirectly open depolarizing channels: ATP activation of P2Y, Substance P activation of NK1, bradykinin activation of B2, glutamate activation of mGlu type I (not shown), and norepinephrine activation of α1 (not shown). Gamma-aminobutyric acid may increase opening of hyperpolarizing chloride channels by binding to GABA-A binding site or indirectly cause opening of hyperpolarizing potassium channels by binding to metabotropic GABA-B receptors. Mu opiate receptors and α2 adrenergic receptors also cause opening of hyperpolarizing potassium channels via activation of metabotropic receptors.

Table 2
Compiled from Refs. 3–6,11,14, and 15

Endogenous ligand	Receptor	Mechanism	Drugs used for pain and pain-related conditions
ATP	P2X	Open Ca^{2+} channels; ATP released in response to tissue trauma	
	P2Y	Bind to Gq protein-coupled receptors to increase intracellular Ca^{2+}, activate platelet aggregation	
Bradykinin	B2 (constitutive) B1 (inducible)	Bind to Gq protein-coupled receptors to increase intracellular Ca^{2+}, increase prostaglandin formation	none
Dynorphin	κ opioid receptor	Gi coupled; linked to dysphoria, hallucinations, and hyperalgesia induced by opioids	Buprenorphine is a mu agonist, kappa antagonist
Endorphin and enkephalin	μ, δ, and κ opioid agonist	Gi coupled; μ and δ receptors increase K^+ efflux	Opiates
GABA	$GABA_A$	Opening of chloride channel	Benzodiazepines
	$GABA_B$	Gi-protein-coupled receptor increases opening of K^+ channel	Lioresal (agonist)
Glutamate	AMPA	Ca^{2+} influx, central sensitization to pain	
	mGLU group I	Gq coupled, Potentiates NMDA activity	
	mGLU group II/III	Gi coupled, indirectly activates K^+ channels and decreases activity of Ca^{2+} channels to reduce nociception; also implicated in central hyperalgesia	
	NMDA	Increases Na^+ and Ca^{2+} influx. Increases activation of AMPA receptors; important in development of hyperalgesia via central sensitization	Dextromethorphan Ketamine Lamotrigine stabilizes Na channel in inactive state and reduces glutamate release
Norepinephrine	α1	Gs coupled, sensitizes nociceptors	
	α2	Gi coupled, reduces calcium influx in presynaptic descending tracts, increases K^+ efflux in secondary postsynaptic neurons	Clonidine
Prostaglandins	Various	Various, dependent upon specific prostaglandin type; increase nociception sensitivity; likely contribute to hyperalgesia	NSAIDs, Aspirin, acetaminophen inhibit prostaglandin formation
Serotonin	5HT3	Increased influx of Na^+ Ca^{2+}; increased activity of AMPA receptors, hyperalgesia	
Substance P	NK1	Gq coupled, leads to increased activity of AMPA/NMDA receptors (short-term sensitization) and increased expression of nociceptors (Long-term sensitization)	

ATP, adenosine triphosphate; GABA, gamma-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug. 5HT3 serotonin receptor subtype are the only known ionotropic serotonin receptors. Actions of serotonin vary widely with receptor subtype.

2. Types of pain

Mechanistically, there are four primary types of pain: nociceptive, inflammatory, neuropathic, and functional pain.[10] Nociceptive pain is usually finite, localized pain that stems from direct activation of nociceptors by noxious stimuli. Tumors can contribute to nociceptive pain by stretching or compressing surrounding viscera and tissues. Neuropathic pain stems from disease

or injury to the peripheral and/or central nervous system. The paresthesias and dysesthesias associated with neuropathic pain are often perceived as a burning or prickling sensation by the patient. Common causes of neuropathy include diabetes mellitus, tumor infiltration,[11] or peripheral damage caused by chemotherapeutic agents.[12] Inflammatory pain represents response to tissue damage and inflammation; inflammatory mediators often heighten nociceptor sensitivity to noxious signals[13] and may play a significant role in the hyperalgesia associated with chronic pain syndromes.[9,14] Functional pain arises from derangements in central processing of incoming pain signals.[11] Chronic pain syndromes are often an amalgam of all four types of pain.

Pain control is maximized and untoward effects are minimized when the medication regimen is targeted to address both the pathophysiologic and mechanistic origins of pain and the patient-specific factors that influence appropriate drug selection. Thus, understanding the pharmacokinetic and pharmacodynamic characteristics of primary and adjuvant agents is essential to optimize pain control.

3. Pain sensitization

Depending upon the type of nociceptive signal and tissue damage, sensitization may lead to heightened pain sensitivity. Sensitization may occur peripherally at the level of signal detection or centrally via increased sensitivity of secondary neurons in the dorsal horn.[2,4,5,15] Changes in the neural milieu may occur over several time scales and on multiple levels. Sensitization may arise from functional alteration of molecules involved in pain perception, transduction, and transmission (e.g., phosphorylation of an ion channel, leading to decrements in its activation threshold) or from structural plasticity (e.g., increased number of synaptic spines).[3]

3.1. Peripheral sensitization

To date, several mechanisms leading to peripheral sensitization have been elucidated. Chronic inflammatory signals lead to decreased activation thresholds and increased responsiveness of peripheral primary afferent neurons, resulting in allodynia, wherein normally innocuous stimuli are perceived as noxious and/or hyperalgesia, which is characterized by noxious stimuli leading to a heightened level of pain perceived for a longer duration compared to the non-sensitized state. Activation of protein kinases by metabotropic receptors (e.g., ATP activation of P2Y receptor subtypes and bradykinin activation of B2 receptors) catalyzes phosphorylation of downstream targets. Phosphorylation of voltage-gated sodium and calcium channels diminishes their activation potential and increases their inward currents,[5] while activation of downstream enzymes turn on the inflammatory signaling cascade. Activation of peripheral receptors also increases the release of neuropeptides (e.g., substance P and cholecystokinin) which in turn causes further activation of inflammatory pathways. Release of neurotrophic factors and activation of second messenger systems can alter expression of various components of pain signaling pathways; both reductions in inhibitory pathway components and increases in excitatory pathway components have been implicated in animal models of peripheral pain hypersensitivity.[16,17] Nonsteroidal anti-inflammatory drugs (NSAIDs), through their ability to inhibit formation of inflammatory mediators of the arachidonic acid pathway, often play a large role in management of peripheral pain sensitization.

3.2. Central sensitization

Sensitization that occurs at the levels of the dorsal horn and central processing is known as secondary or central sensitization. Like peripheral sensitization, central sensitization may result in allodynia and/or hyperalgesia.[2,3,5] While there is some overlap in the peripheral and central pathways that lead to sensitization, synaptic transmission in the spinal cord is modulated by

both local interneurons and, as discussed earlier, by projections that descend from the brainstem to the dorsal horn. Figure illustrates that synaptic transmission in the dorsal horn between primary afferents and secondary projection neurons occurs by rapid ligand-gated ion channel transmission and by slower metabotropic pathways. The primary ion channels involved in this synaptic transmission are the glutamate-activated AMPA receptor subtypes.[2–5,15] NMDA-type receptors are present on the postsynaptic membrane but under healthy circumstances are kept quiescent by magnesium ions that block the associated calcium channels. Glutamate also activates the metabotropic mGLU receptors; other slow modulatory pathways are activated by neuropeptides {substance P, calcitonin gene-related peptide (CGRP)}, and neurotrophic factors {e.g., brain derived neurotrophic factor (BDNF)}; downstream effects of these slower signals induce, via phosphorylation, a conformational change in the NMDA receptor which causes dissociation of the blocking magnesium ions. The flow of calcium current through the NMDA-gated calcium channel leads to multiple downstream events, including further activation of AMPA receptors,[2,3] activation of extracellular signal-related protein kinase (ERK, also known as mitogen-activated protein kinase-1 or MAPK1),[4,5] activation of neuronal nitric oxide synthetase, activation of neuronal cyclooxygenase (COX),[4] and activation of other calcium-sensitive transcription factors.[5] This sequence of events leads to glial activation, production of inflammatory cytokines, generation of reactive oxygen species, and increased sensitivity to incoming nociceptive signals that often outlast the initial triggering event.[15] NMDA receptor antagonists such as ketamine and dextromethorphan may mitigate NMDA receptor-mediated sensitization, but due to the wide distribution of NMDA receptors, side effects such as psychosis and amnesia limit such utility. Subanesthetic doses of ketamine may produce a balanced analgesia without major dysphoric effects.[18] Activation of the cannabinoid CB1 and CB2 Gi-protein-coupled receptors may reduce central hyperalgesia by reducing MAPK1 signal transduction.[4]

Opiates used to produce analgesia may actually contribute to central pain sensitization to the level that the patient experiences increasing pain as the opiate dose is escalated.[15,19,20] Opioid-induced hyperalgesia likely involves sensitization of both central and peripheral pathways.[19,20] The etiology of opiate-induced hyperalgesia is multifactorial and not yet completely understood, but current evidence points to five primary components: central glutamate signaling, spinal opiate dynorphins, facilitation of descending tracts, genetic susceptibility, and alterations in expression of components in nociceptive signaling, transduction, transmission, and perception.[19] In the context of palliative pain management, it is of particular importance to recognize the potential of opioids to induce hyperalgesia. Clinical aspects of opioid-induced hyperalgesia are discussed in the opioid section below.

4. Treatment of chronic pain

4.1. American Pain Society: Five critical factors for quality pain management

In 2005, the American Pain Society determined that attention to five areas is critical for consistent quality in the delivery of pain relief.[21] In their recommendations, they advocate that providers recognize and treat pain promptly; include patients and their caregivers in pain management planning; provide multimodal therapy to address pain type, etiology, and factors that alter pain perception; frequently adjust treatment based upon continuous reassessment of pain quality, intensity, and adverse effects; and monitor the outcomes using national performance indicators.

The World Health Organization's analgesic ladder, developed in the 1980s, has widely influenced many strategies used to manage chronic pain. While the ladder itself is not an evidence-based tool, several evidence-based guidelines have been developed using the analgesic ladder as a basis.[22–25] The "ladder" is a stepwise approach to pharmacologic management of pain, beginning with non-opioid agents for mild pain and progressing through "weak" opioids to "strong" opiates for the management of severe pain.[26] Adjunctive agents are added as needed at any step.

4.1.1. Step 1: Non-opioids for mild pain

Non-opioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are foundational to the WHO analgesic ladder and are recommended alone or in combination with adjuvants for mild to moderate pain and in conjunction with opioids for more severe pain. These agents may be administered as needed or around-the-clock, with upward dose titration as needed.[26,27] As mentioned previously, NSAIDs may ameliorate pain hypersensitivity syndromes by reducing prostaglandin formation. Table 3 provides a summary of step 1 non-opioid drugs currently available in the United States.

Acetaminophen is a non-prescription medication that is generally safe when used in limited doses, though it does have a relatively narrow therapeutic index due to its propensity to induce hepatotoxicity.[28] Acetaminophen, also known as paracetamol, provides antipyretic and mild analgesic effects with limited risk of the adverse gastrointestinal, cardiovascular, or antiplatelet effects associated with NSAIDs. Acetaminophen also lacks the anti-inflammatory benefits associated with NSAIDs.[28] It is believed that acetaminophen produces its analgesic effects via inhibition of central prostaglandin formation, but the exact mechanism of acetaminophen action has not yet been confirmed. Likewise, evidence of benefits when combined with opioids for moderate to severe pain is lacking.[29–31] Current United States Food and Drug Administration (USFDA) recommendations for acetaminophen include a maximum daily dose of 4 g in healthy patients,[27] though mandates have recently been issued to reduce the risk of acetaminophen-related hepatotoxicity. Particular caution is advised for patients taking multiple products containing acetaminophen, those with underlying hepatic disease, and those who consume more than three alcoholic beverages per day.[32]

NSAIDs offer effective pain management as monotherapy for patients with mild pain in step 1.[28] Evidence shows that NSAIDs added to step 3 opioids confer greater efficacy,[31,33] particularly for patients with an inflammatory[34] or hypersensitivity[15] component to their pain profile and for those with bone pain.[35] However, serious toxicities limit the use of NSAIDs (including aspirin) in pain management.

NSAIDs produce their anti-inflammatory, analgesic, and antipyretic effects by inhibiting COX, the first enzyme involved in the formation of prostaglandins from arachidonic acid.[36] There are two known forms of COX, COX-1 and COX-2. COX-1 is predominantly constitutively expressed and produces many prostaglandins required for basic cellular housekeeping functions such as maintaining the protective mucosa of the gastric epithelium. Expression of COX-2 is largely induced by inflammatory signals. NSAIDs vary in their selectivity for these two COX isoforms; COX-2 inhibitors were designed to minimize the risk of gastric erosions.[37]

The selectivity for the two COX isoforms appears to be one factor that impacts the adverse effect profile. The COX-2-selective agent celecoxib poses approximately half the risk of GI erosion[38] but poses a greater risk of thrombotic events.[33] Formation of the pro-aggregant thromboxane A2 (TXA2) is catalyzed by COX-1, while formation of the anti-aggregant prostacyclin (PGI2) is catalyzed by COX-2. Thus, selective inhibition of COX-2 often induces thrombotic events by promoting platelet aggregation.[34,36]

All NSAIDs pose some risk of gastritis and/or GI erosion.[33] Risk factors for NSAID-induced GI ulceration include older age ($>$ 60 years), concomitant steroid use, ethanol use ($>$ 3 drinks/day), history of peptic ulcer disease, major organ dysfunction, long-term NSAID use, *Helicobacter pylori* infection, and SSRI use.[22,36,37,39] Degree of COX selectivity is associated with risk of GI ulceration. Ketorolac is an NSAID with predominant COX-1 activity; the risk of GI ulceration with this agent is so great that the USFDA does not recommend its use beyond 5 days.[36] Most NSAIDs can also cause gastritis; it is important for patients to understand that NSAID-induced ulcers are rarely preceded by symptoms of GI distress.[35] The relative GI protection gained from selective inhibition of COX-2 is lost when aspirin is used concomitantly.[35]

NSAID and COX-2 inhibitors increase renal reabsorption of chloride ion and increase the activity of vasopressin by suppressing prostaglandin inhibition.[35] Loss of prostaglandin-mediated dilation of the glomerular afferent arteriole also contributes to loss of glomerular filtration and hypertension.[40] Patients over 60 years of age and those with hypovolemia, diabetes mellitus, multiple myeloma, hyperadrenal states (e.g., congestive heart failure),

Table 3
Systemic non-opioid drugs available in the United States.[22,27,28,31–36,38,44]

COX selectivity	Drug	Dosing	Maximum mg/day	Comments
More COX1 selective	Ketorolac	15–30 mg IV every 6 h; lower dose in patients > 65 years	120 < 65 60 > 65	Not to exceed 5 days due to severe GI risk; acute use only
	Flurbiprofen	50–100 mg every 6–12 r	300	
	Ketoprofen	25–50 mg every 6–8 h	300	Hepatotoxic risk
	Indomethacin	25–50 mg every 8 h or 75 mg sustained release every 12 h	150	GI and CNS risks high
	Tolmetin	1.2–1.8 g/day in 3 doses	1800	
	Aspirin	325–650 mg every 4–6 h	4000	High GI risk; maximal impact on inhibition of platelet function
	Nabumetone	1–1.5 g/day in 1–3 doses	2000	Once daily dosing feasible
	Fenoprofen	800–3200 mg/day in 4 doses	3200	
	Meclofenamate	50–100 mg every 4–6 h	400	
	Sulindac	150–200 mg every 12 h	400	Hepatotoxic risk
	Naproxen	750–1000 mg base or 825–1100 mg Na in 2–3 doses	1250 1375	Appears to carry lowest risk of cardiotoxicity
	Piroxicam	10–20 mg every 24 h	20	High GI risk
	Oxaprozin	1200 mg daily	1800	Hepatotoxic risk
	Ibuprofen	400 mg every 4 h	3200	Less GI risk with doses < 2400 mg/day; less cardiotoxic risk
	Acetaminophen	650 mg every 4 h or 1 g every 6 h (FDA is currently evaluating daily maximum dose)	4000	Dose dependent hepatotoxicity; Caution when using combination opioid-acetaminophen products; no anti-inflammatory effects; minimal GI risk; minimal impact on platelet function
	Choline magnesium trisalicylate	1.5–4.5 g/day in 3 doses	3000	Minimal impact on platelet function; less risk of gastropathy compared to many other NSAIDs; often tolerated in asthmatics; less renal toxicity
	Salsalate	2–3 g/day in 2–3 doses	3000	
	Diflunisal	1–1.5 g/day in 2–3 doses	1500	
	Meloxicam	7.5–15 mg every 24 h	15	Less selective at higher dose
	Diclofenac	150 mg/day in 3 doses	150	
	Celecoxib	200 mg/day in 1–2 doses	400	Less GI risk, high cardiovascular risk
More COX2 selective	Etodolac	600–1000 mg/day in 3–4 doses	1000	

concomitantly administered nephrotoxins, underlying renal disease, and concomitant blockade of angiotensin, and those receiving renally cleared chemotherapeutic agents are at greatest risk for renovascular and hypertensive effects from inhibitors of prostaglandin formation.[33] Monitoring of fluids, electrolytes, renal parameters, and blood pressure is essential to detect adverse renal effects from NSAIDs. Nonacetylated salicylates and sulindac are associated with a diminished incidence of renal impact, though they may not provide the same level of pain management as other NSAIDs.[22] NSAIDs are also associated with allergic nephritis and analgesic nephropathy.[35]

Inhibition of COX-1 may decrease platelet aggregation, while inhibition of COX-2 increases aggregation. Agents with more selectivity toward COX-2 are associated with a greater risk of myocardial infarction, stroke, and other thrombotic events.[41–43] At the opposite end of the spectrum, agents that significantly inhibit COX-1 pose a risk for patients with thrombocytopenia or those suffering from other hematologic toxicities. Use of COX-2-selective agents and nonacetylated salicylates may be preferred in this setting[34,37]

Despite the risks, NSAIDs offer significant pain relief for milder pain and may reduce opioid-related side effects through their opioid-sparing properties when used in combination with opiate receptor agonists.[34] Careful monitoring is required to minimize adverse sequelae from NSAID use. Table 3 details adverse effect profiles and risk factors associated with NSAIDs and special concerns and dosage recommendations for individual agents.

4.1.2. Step 2: "Weak" opioids for moderate pain

In the original inception of the WHO guidelines, "weak" opioids were added in step 2 of the WHO analgesic ladder to manage moderate to severe pain not managed by routinely scheduled doses of non-opioids alone. While the analgesic ladder has not changed, classification of opiates as "weak" or "strong" is no longer recommended but will be used throughout this section. Codeine is the prototypical "weak" opioid; other agents considered as "weak" agonists include the opioid/non-opioid combinations hydrocodone with acetaminophen and oxycodone with acetaminophen, mixed action agents tramadol and tapentadal, partial agonist buprenorphine, and the mixed agonist/antagonists butorphanol and nalbuphine. Full agonist opioid/non-opioid combinations are generally preferred step 2 agents,[44] though some evidence exists to support the use of tramadol[45] and transdermal buprenorphine.[46]

Use of "weak" opioids has several limitations. Generally, mixed agonist/antagonist or partial agents are not used because their maximum daily dose is limited by a ceiling[47]; dosing beyond this ceiling provides no additional pain relief. Furthermore, mixed agonist/antagonists may precipitate abstinence syndrome in opiate-dependant patients.[44] Most opioid/non-opioid combinations contain acetaminophen, which limits the total daily dose that may be administered. Codeine requires activation by conversion to its active metabolite morphine, a reaction that is catalyzed by cytochrome oxidase P450 isoform 2D6. This activation pathway renders codeine less effective in patients who are phenotypically "poor metabolizers" via 2D6 and in those who concomitantly take strong 2D6 inhibitors such as fluoxetine.[48] Tramadol is a weak mu agonist that blocks the presynaptic reuptake of both serotonin and norepinephrine. These antidepressant-like effects may offer relief for neuropathic types of pain but contribute to a risk of seizures or serotonin syndrome. Use of a routinely scheduled low-dose of "strong" opioid at step 2 is an alternative that can be used to avoid these many pitfalls.[49] Table 4 details step 2 and step 3 opioids.

4.1.3. Step 3: "Strong" opioids for moderate to severe pain

Full mu opioid receptor agonists comprise the "strong" opioid rung of the WHO analgesic ladder. Morphine is the standard opiate agonist against which all others are compared, largely due to its long history of use, known effectiveness, and low cost.[48,50] There is little evidence to suggest that any significant differences exist regarding activity of full mu opiate receptor agonists (MOR), and with the exception of meperidine and methadone, there is likewise little evidence to suggest that side effect profiles vary significantly between full mu opiate receptor agonists.[49,50] Unlike agents recommended for use in steps 1 and 2, full MOR agonists, with the exception of meperidine and codeine, do not exhibit a dose-related ceiling[5,51–53]; meperidine is not recommended for use in the management of chronic pain.

There is a significant amount of individual variation in response to individual agents,[53] and the products are available in the US in various dosage forms. Table 4 details step 2 and step 3 opioids agents available for use in palliative pain management. Methadone is a unique long-acting[28,49] agent with multiple pharmacodynamic effects: full mu opiate receptor agonism, NMDA receptor antagonism,[28,50,54] and monoamine-reuptake blockade.[54] Methadone has a long and unpredictable elimination half-life and may prolong the QTc interval.[28,50,54] Clearance of methadone is largely hepatic via cytochrome oxidase P450 3A4 catalysis[5]; it is not likely to accumulate in renally compromised patients. However, due to its unpredictable pharmacodynamic and pharmacokinetic nature, expert consultation is recommended prior to use of methadone.[22]

4.2. Initiation and titration of opioids

Appropriate assessment of the patient's pain is germane to pain management at any level and at every encounter.[22,25,51] All patients with pain should be assessed with regard to pain location, type, intensity, quality, onset/duration, the patient's definition of pain, presence of concomitant psychological disorders, and actions that relieve/worsen pain, including previous analgesic drug

Table 4
Step 2 and 3 opioids available in the United States.

Drug	DEA*	Special considerations	Dosing interval
Step 2: opioids for moderate pain			
Buprenorphine	C-III	Partial agonist generally not recommended, but evidence supports use of transdermal patch.[47] Upper dose limited by efficacy. May precipitate withdrawal in opioid-dependant patients	Patch: every 7 days IV: every 6–8 h
Butorphanol	C-IV	Mixed agonist/antagonist use generally not recommended. Reduce dose and extend interval to every 6 h in renal aal and severe hepatic impairment. Upper dose limited by efficacy.	IV: every 3–4 h
Codeine and acetaminophen	C-III	Efficacy impaired in low-capacity CYP450 2D6 phenotype; upper dose limited by acetaminophen content. Avoid in hepatic impairment.	PO: every 4–6 h
Hydrocodone with acetaminophen	C-III	Upper dose limited by acetaminophen content. Avoid in hepatic impairment.	PO: every 4–6 h
Nalbuphine		Mixed agonist/antagonist use generally not recommended.[22] Upper dose limited by efficacy. May precipitate withdrawal in opioid-dependant patients.	IV: every 3–6 h
Tapentadol	C-II	Upper dose limited by toxicity	PO immediate release: every 4–6 h PO extended release: every 12 h
Tramadol		Upper dose limited by toxicity; Maximum dose in patients over 75 years of age: 300 mg/day; Renal impairment (Cl_{cr} < 30 mL/min): maximum 200 mg/day— avoid extended release; *Hepatic impairment*: immediate release maximum 50 mg every 12 h—avoid extended release	PO immediate release: every 4–6 h PO extended release: once daily
Step 3: opioids for moderate to severe pain; equianalgesic dose is included with drug name[22]			
Fentanyl Transdermal see Table 5	C-II	Not intended for use in opioid-naïve patients. Deaths have occurred when patients applied more than one patch, applied patches more frequently than ordered, or when exposing application site to external sources of heat. Transmucosal immediate-release fentanyl products are available only through the Transmucosal Immediate-Release Fentanyl (TIRF) REMS access program. Enrollment is required for outpatients, prescribers, pharmacies, and distributors. See www.TIRFREMSaccess.com for more information. Reduce dose by 50% in mild to moderate hepatic or renal impairment; not recommended in severe renal or hepatic impairment.	Transmucosal as needed (see individual product prescribing information for detailed information): Lozenge: 4 h Buccal film: 2 h Buccal tablet: 4 h Nasal spray: 2 h Sublingual spray: 4 h Sublingual tablet: 2 h Transdermal (around-the-clock): 72 h
Hydromorphone IV 1.5 mg PO 7.5 mg	C-II	Less problematic in patients with renal impairment. Initiation at 25–50% of usual starting dose recommended in patients with hepatic and/or renal Providers who prescribe Exalgo® extended-release tablets are required to receive training. See www.exalgorems.com for further information.	IV: every 1–4 h PO Immediate release: every 2–4 h Controlled release: every 12 h Extended release: every 24 h

Table 4 (*continued*)

Drug	DEA*	Special considerations	Dosing interval
Levorphanol IV 2 mg PO 4 mg	C-II	In addition to full mu opioid receptor agonism, possesses some NMDA antagonist activity. Dosage reduction recommended for renal and/or hepatic impairment.	IV: every 3–6 h PO: every 6–8 h MAY ACCUMULATE, increase interval
Methadone VARIABLE	C-II	In addition to full mu opioid receptor agonism, possesses some NMDA antagonist and monoamine oxidase inhibiting activities. Conference with pain specialist recommended. Reduce dose by 50–75% in severe renal impairment ($Cl_{cr} < 10$ mL/min); avoid in severe hepatic disease.	PO: every 8–12 h
Morphine IV 10 mg PO 30 mg	C-II	Active metabolite may accumulate in patients with renal dysfunction; Cl_{cr} 10–50 mL/min reduce dose by 25% $Cl_{cr} < 10$ mL/min reduce dose by 50%. Excessive sedation may occur in patients with cirrhosis	Subcutaneous: every 4 h or continuous Intravenous: every 3–4 h PO Immediate release: every 4 h Controlled-release tablet: every 12 h Extended-release capsule: every 24 h Sustained-release capsule: every 12 or 24 h Rectal: every 3–4 h
Oxycodone PO 15–20 mg	C-II	Manufacturer recommends dosage adjustment for sustained-release formulations be performed by adjusting dose, not dosing interval. Sustained-release formulations are not for "as needed" use, but should be dosed around-the-clock. The oral solution is available as both 1 mg/mL and 20 mg/mL concentrations; care should be taken to prevent potential dosing errors. As a requirement of the REMS program, healthcare providers who prescribe OxyContin must receive proper training. See www.oxycontinrems.com for more information. Reduce dose in renal impairment based upon clinical picture.	Oral only Immediate release: every 4 h Controlled release: every 12 h
Oxymorphone IV: 1 mg PO: 10 mg	C-II	Manufacturer warns that extended-release formulation is not suitable for "as needed" use, but should be dosed around-the-clock.	IV: every 3–6 h PO Immediate release: every 4–6 h Extended release: every 12 h

NOTE: Extended-release formulations are not intended for as needed or rescue doses.

* US Drug Enforcement Agency Scheduled Drug Classification.

history.[33,51] The use of visual analog scales, verbal rating scales, and numeric rating scales helps to guide pain management regimens by quantifying pain intensity.[51,55] Published guidelines recommend utilizing a 10-point scale to guide initiation of pain pharmacotherapy.[25,51] The National Comprehensive Cancer Network designates scores between zero and three as mild pain, scores between four and six as moderate pain intensity, and those between seven and 10 as severe.[25] Additionally, it is important to identify the source of pain in order that a disease modifying therapy may be initiated to address the cause of pain specifically.

Specific to use of opioids, both patients' concerns about addiction and their risk for addiction should be assessed. It is imperative to recognize that many patients undergoing extended pain management with opioids will become tolerant to and dependent upon opioids without developing addiction. According to the Institute for Clinical System Improvement, addiction may be defined as a "chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."[33] It is also important to understand that the legal concept of drug diversion is synonymous with neither addiction nor dependence. The Federal Controlled Substances Act states that prescribers must cease prescribing controlled substances when they identify a strong likelihood that the prescribed drug is being diverted into the illicit marketplace; it is lawful under federal policy to prescribe, administer, and/or dispense controlled substances for "legitimate medical purposes such as the relief of pain, muscle spasms[,] and anxiety"[56] for patients who are or were addicted/substance abusers. There are several tools used to assess risk and assist in identification of aberrant drug use.[33,57]

As discussed later, long-acting (LA) or extended-release (ER) formulations of oral opioids are often the mainstay of palliative pain management regimens. These sustained-release formulations contain more medication per dispensing unit compared to prompt-release formulations and are therefore associated with a greater risk of overdose. Under the authority of the Food and Drug Administration Amendments Act of 2007, the USFDA announced in April 2011 that these long-acting dosage forms would be required to have a Risk Evaluation and Mitigation Strategy (REMS) to reduce the risks associated with use of LA/ER opiate formulations.[58] On July 9, 2012, the USFDA approved the REMS for ER/LA opioids.[59] This REMS includes the requirements that (1) a Medication Guide be dispensed with each ER/LA opioid analgesic prescription; (2) sponsors of ER/LA opioids will provide grant monies to fund accredited continuing medical education programs available to all Drug Enforcement Agency (DEA)-registered prescribers in accordance with the USFDA Blueprint for Prescriber Education; and (3) prescribers will be provided with a patient counseling document to give to patients to help assure that prescribers properly counsel patients on their responsibilities for safe use and appropriate disposal of these medications.

Despite the risks associated with opiates, practitioners should have a low threshold to prescribe opioids in palliative care.[44] If opioid therapy is initiated with a step 2 opioid, a switch to a pure opioid preparation will be required if dose escalation is necessary to provide adequate analgesia.[22] Fixed-interval dosing (i.e., a regular dose at a scheduled time) is more effective than on-demand or *pro re nata* (prn or as needed) dosing.[22,51,60] Traditionally, short-acting opiates have been recommended for initiation of chronic pain management,[27,61] but there is now evidence to support the use of sustained-release (LA/ER) products combined with prompt-release coverage of breakthrough pain.[25,55] Immediate-release oral formulations of most opiates require frequent (i.e.; every 4 h) administration, while ER/LA facilitate adherence by reducing basal dosing to once or twice daily depending upon the specific drug formulation.[51] The convenience of ER/LA formulations is offset by delays in management of pain due to slow onset and subsequent delays in dosage adjustment.

As previously mentioned, morphine is the mu agonist against which all others are compared for equianalgesic dosing, though its variable oral bioavailability, dependence on renal function for clearance of parent drug and active metabolites, and widely variable dose-response relationship render it a less-than-ideal opiate.[50] Orally administered drugs are considered first-line for patients who can tolerate oral medications. Respiratory depression may occur, especially in opiate-naïve individuals; therefore assessment of prior opiate exposure is critical when

initiating opiate therapy. A patient is considered opiate tolerant after 1 week of continuous dosing of transdermal fentanyl patch of 25 mcg/h, oral oxycodone of 30 mg/day, oral hydromorphone of 8 mg/day, or oral oxymorphone of 25 mg/day.[63] During initial titration in opiate-naïve patients, parenteral dosing will provide the most rapid titration and prompt-release oral formulations will provide fairly rapid relief, while use of sustained-release products with prompt-release coverage of breakthrough pain may delay dose optimization. Maximum analgesic effect from any repeated dosing strategy will not be achieved until steady-state drug levels are achieved (approximately 5 elimination half-lives); if dosing adjustments are made before steady-state levels are achieved, drug accumulation may occur with subsequent risk of respiratory depression. The following dosages are recommended for initiation of morphine in opiate-naïve patients with normal hepatic and renal function:

- Parenteral[22]: 2–5-mg morphine sulfate or equivalent.
  - IV: reassess efficacy and adverse effects at 15 min.
  - Subcutaneous: reassess efficacy and adverse effects at 30 min.
    - Pain score decreased to 0–3/10 without adverse effect: continue dose at appropriate interval (Table 4) with frequent assessment for adverse effects.
    - Pain score decreased to 4–6/10: repeat same dose at appropriate interval for two or three doses, if pain not diminished, consider (1) titrate dose upward by 25–50% and reassess; (2) assess and treat/adjust dose of adjuvant agents for specific pain syndromes; and (3) interventional strategies or specialty consultation.
    - Pain remains at 7–10/10: (1) increase dose by 50–100% with appropriate reassessment and consider; (2) assess and treat/adjust dose of adjuvant agents for specific pain syndromes; and (3) consider interventional strategies or specialty consultation.
- Immediate-release oral[22]: 5–15 mg oral morphine or equivalent. Assess efficacy and adverse effects at 60 min.
  - Pain score decreased to 0–3/10 without adverse effect: continue dose and assess for adverse effects.
  - Pain score decreased to 4–6/10: repeat same dose × 2–3; if no relief, consider increase by 25–50% with reassessment at 60 min.
  - Pain score remains at 7–10/10: increase dose by 50–100% with appropriate reassessment and consider (1) assess and treat/adjust dose of adjuvant agents for specific pain syndromes and (2) interventional strategies or specialty consultation.
- Sustained-release oral[25]: Morphine SR 10–15 mg or equivalent every 12 h with 5 mg immediate-release morphine equivalent every 1–2 h as needed for breakthrough pain. Assess efficacy and adverse effects at 48 h.
  - Pain level is 0–3 without adverse effect and minimal rescue doses used: continue current regimen with frequent monitoring.
  - Pain level is 4–6/10 OR 3 or more breakthrough doses have been used: add total daily dose taken.
    - Add total mg amount of drug taken over initiation period.
    - Divide by number of days in monitoring period (calculate average daily mg dose of drug taken).
    - Divide this by the number of ER/LA doses indicated by selected drug formulation (e.g., by 2 for formulations that require a 12-hour dosing interval).
    - Round up or down to dose achievable by product availability (e.g. 25 mg oxycodone SR q12 h, round to 20 mg q 12 h).
    - Add 5–15% of the new total daily dose q 1–2 h as needed for breakthrough pain.[63]
  - Pain level is 7–10/10: consider switching to parenteral or immediate-release formulation for titration.[50]

For patients who have been on chronic opioids previously and require upwards titration due to tolerance (see “management of adverse effects” later for a discussion about tolerance versus hyperalgesia), the initial titration dose is based upon the previous total daily dose. This strategy

is of particular importance to patients started on a step 2 opioid who require titration above the step 2 ceiling dose.

- Parenteral[21]: Administer opioid dose equivalent to 10–20% of total daily opioid dose in previous 24 h. Assess for efficacy and adverse effects at 15 min.
  - Pain score decreased to 0–3/10 without adverse effect: continue dose at appropriate interval (Table 4) with frequent assessment for adverse effects.
  - Pain score decreased to 4–6/10: repeat same dose at appropriate interval for two or three doses and if pain does not diminish, consider (1) titrating dose upward by 25–50% and reassess; (2) assess and treat/adjust dose of adjuvant agents for specific pain syndromes; and (3) interventional strategies or specialty consultation.
  - Pain remains at 7–10/10: increase dose by 50–100% with appropriate reassessment and consider (1) assess and treat/adjust dose of adjuvant agents for specific pain syndromes and (2) interventional strategies or specialty consultation.
- Immediate-release oral: Administer oral opioid dose equivalent to 10–20% of total opioid taken in the previous 24 h. Reassess efficacy and adverse effects at 60 min.
  - Pain score decreased to 0–3/10 without adverse effect: continue dose and assess for adverse effects.
  - Pain score decreased to 4–6/10: repeat same dose × 2–3; if no relief, consider increase by 25–50% with reassessment at 60 min.
  - Pain score remains at 7–10/10: increase dose by 50–100% with appropriate reassessment and consider (1) assess and treat/adjust dose of adjuvant agents for specific pain syndromes and (2) interventional strategies or specialty consultation.

4.3. Establishing realistic goals

Most patients will consider pain management to be effective if it decreases their pain intensity by 33–50%.[64–67] Including the patient and/or patient caregiver in establishing a reasonable goal (i.e.; a reduction of pain intensity by 33–50% based upon objective measurement) is critical to patient satisfaction and reduction in suffering.[22] The appropriate dose of a full mu opiate receptor agonist is the dose that adequately relieves the individual patient's pain throughout the dosing interval without causing unmanageable adverse effects.[22] Special caution is required when initiating opiate therapy in patients with COPD, sleep apnea, heart failure, and renal or hepatic dysfunction. Table 4 identifies special considerations of various comorbid states. Just as doses are titrated upwards in times of pain escalation, downward titration may be considered when pain is quiescent. Reductions of 10–25% in total daily dose every five to six half-lives is considered reasonable, with frequent assessment for signs of withdrawal or pain escalation.[22]

Patients must be monitored very closely for adverse effects of opiate therapy, and these effects should be aggressively managed. Maximization of step 1 non-opioids and adjuvant agents often provides an opioid-sparing effect. Fortunately, tolerance to many opioid side effects may develop over time; constipation is one effect that does not.[60,61] Prophylaxis for constipation should be initiated with initiation of opioid medications.[22]

4.4. Detection, prevention, and management of opioid adverse effects

4.4.1. Constipation

Constipation is probably the most common adverse effect of opiates. It is best prevented by combining good bowel hygiene with prophylactic pharmacologic agents.[22,68] The G-protein-coupled mu opioid receptors exist in high density in the gastrointestinal tract; stimulation of these receptors reduces forward motility, leading to longer fecal dwell times and increased reabsorption of water with subsequent constipation.[60] Appropriate bowel hygiene includes adequate intake of dietary fiber and fluid combined with exercise if possible. Addition of bulk-forming laxatives (e.g., psyllium) is generally not recommended.[22] Suggested pharmacologic

agents for prophylaxis of constipation include osmotic agents (e.g., lactulose[68] and polyethylene glycol)[22] or a stimulant laxative (e.g., senna) with or without a stool softener (e.g., docusate).[22,28] A reasonable goal for patients on opioid therapy is three bowel movements per week.[28]

If constipation does occur, fecal impaction and obstruction must first be ruled out, and other contributory causes should be addressed.[22] Initial treatment of constipation generally consists of a stimulant/laxative stool softener titrated to effect of a non-forced bowel movement every 1–2 days.[22] If impaction exists, a glycerin suppository with or without mineral oil retention enema may be attempted; if unsuccessful, manual disimpaction (after analgesic ± anxiolytic) should be attempted.[22]

If constipation is persistent, combinations of laxatives that act through different mechanism (osmotic + stimulant + lubricant) may help maintain bowel function; addition of a prokinetic agent such as metoclopramide 10–20 mg four times daily may also provide relief.[22] Alternatively, methylnaltrexone is a peripherally acting mu receptor antagonist that has been approved for use in the treatment of opioid-induced constipation for palliative care patients who have had inadequate response to other laxation attempts.[28,69] It is administered subcutaneously at a dose of 0.15 mg/kg every other day as needed; use beyond 4 months has not been studied. For convenience, the drug is available in prefilled syringes: 8 mg/0.4 mL for patients between 34 and 136 pounds exclusively and 12 mg/0.6 mL for patients between 135 and 252 pounds exclusively; single use vials containing 12 mg/0.6 mL should be used for patients outside these body weight ranges.[70] For those patients on chronic opioid therapy and intractable constipation, conversion to transdermal fentanyl[22,61] or methadone[22] may help mitigate constipation (see later, interconversion of opiates for details on dosage conversion). While there is a lack of current evidence to support rotation to opiates other than transdermal fentanyl and methadone, such rotation is supported by expert opinion.[28]

4.4.2. Nausea and emesis

Constipation is often one of the underlying causes of opioid-related nausea and emesis, so proper attention to bowel function often reduces this troublesome GI complaint. Other remediable contributors include hypercalcemia and other electrolyte disturbances, meningeal irritation, cancer chemotherapy and radiation therapy, gastroparesis, anxiety, dopaminergic drugs in the treatment of Parkinson's disease, and other medication-related causes.[22,69–71] Furthermore, nausea and vomiting very frequently decrease quality near the end of life, with up to 60% of advanced cancer patients suffering to some degree.[72] For patients taking opioids, several pharmacologic options for management of nausea and emesis are available once other contributory causes have been addressed. Nausea is generally provoked by activation of dopamine, histamine, acetylcholine, and serotonin 5HT3 receptors in the chemoreceptor trigger zone of the area postrema (a circumventricular organ that is outside of the blood–brain "barrier") and the GI tract.[5] It is therefore not surprising that most antiemetics act to antagonize these receptors. Blockade of the central dopamine D2 receptor can cause extrapyramidal effects such as dystonia and akathisia; D2 antagonists are relatively contraindicated in patients with Parkinson's disease.[73] Haloperidol is an example of a drug that is very selective for central dopamine D2 receptor blockade; it is generally dosed for nausea at 0.5–4 mg orally, subcutaneously, or IV every 6 h. In addition to antagonizing dopamine D2 receptors in the chemoreceptor trigger zone receptors, older phenothiazines such as prochlorperazine, chlorpromazine, and promethazine produce beneficial and adverse effects through their actions as antagonists at H1 histamine and M3 muscarinic receptors and additional adverse effects through blockade of adrenergic α1 and sodium channels.[5,73,74] Sedation is the primary adverse effect associated with histamine H1 blockade. Blockade of muscarinic M3 receptors can cause xerostomia, delirium, urinary retention, and constipation.[5,73,74] Adrenergic alpha 2 blockade increases fall risk due to postural hypotension, while blockade of sodium channels can lead to cardiac dysrhythmias.[74] Prochlorperazine is very commonly used for nausea, dosed at a rate of 10 mg orally every 6 h as needed. Promethazine is occasionally used at a dose of 12.5–25 mg orally every 6 h as needed. Metoclopramide produces its beneficial effects through several

mechanisms, including antagonism of dopamine D2 receptors in the GI tract and the area postrema, antagonism of serotoninergic 5HT3 receptors (at higher doses), activation of serotonin 5HT4 receptors in the GI tract, and stimulation of muscarinic receptors in the GI tract.[75] These actions add the benefit of increased GI motility which may improve constipation, but dopamine blockade poses a risk of extrapyramidal adverse effects.[75] Metoclopramide is usually dosed at 10–20 mg orally or IV every 6 h as needed. Dolasetron, granisetron, ondansetron, and palonosetron are serotonergic 5HT3 receptor antagonists that work to block receptors in the GI tract and area postrema.[75] These agents are generally well tolerated but may contribute to constipation.[22] Granisetron and ondansetron are most commonly used to control opiate-induced nausea and emesis; granisetron is dosed at 2 mg orally daily, while ondansetron is dosed at 8 mg orally three times daily[22]; both of these agents are also available for parenteral administration, and ondansetron is additionally available as an orally disintegrated tablet (ODT). Finally, dexamethasone may offer some relief of nausea, presumably due in part to its ability to reduce inflammation in the meninges.

4.4.3. Pruritis

Opiates can cause pruritis by both direct actions on sensory neurons and non-immunologic mast cell release of histamine.[5] If itching is associated with a rash or hives, selection of an opioid from another chemical class may be warranted[21,76] (see opiate allergy later). There are two pharmacologic approaches most commonly used to address non-allergic pruritis: histamine H1 blockade and low-dose opiate receptor antagonism. The dopamine D2 antagonist promethazine is often used to address opiate-induced pruritis at the same dosing rate as for its antiemetic effect. Diphenhydramine antagonizes histaminic H1 and muscarinic M3 receptors, thereby producing potential antipruritic and nausea benefits with risk of adverse effects such as sedation, xerostomia, urinary retention, and constipation.[22] Diphenhydramine is generally dosed as 25–50 mg IV or orally every 6 h as needed. If neither of the above options is efficacious, opioid rotation may relieve pruritis, or addition of nalbuphine may be attempted. Nalbuphine is an opiate agonist/antagonist that may be dosed at 0.5–1 mg IV every 6 h as needed. A slow continuous infusion of the full opiate antagonist naloxone may provide relief without disruption of pain control and without emergence of withdrawal symptoms. It is generally started at a rate of 0.25 mcg/kg/h and titrated to effect up to a maximum of 1 mcg/kg/h.[22]

4.4.4. Delirium

Opiates are one possible cause of delirium in palliative care patients. After ruling out other causes of delirium (e.g., hypercalcemia and other medications), either opioid rotation or addition of an adjuvant with subsequent downward titration of opiate should be attempted. If neither of these options is effective, a trial of dopamine antagonist is warranted. Three agents are predominantly used: haloperidol (0.5–2 mg PO or IV every 4 h as needed), risperidone (0.25–0.5 mg PO q 12–24 h as needed), or olanzapine (2.5–5 mg PO or SL every 6 h as needed).[22,77] Haloperidol and risperidone lack the antimuscarinic effects associated with many older dopamine antagonists, thus may be preferred in delirium due to the propensity of antimuscarinics to contribute to delirium, especially in elderly patients.[78]

4.4.5. Respiratory depression

At therapeutic levels, opiates generally impact respiratory rate. At toxic levels, tidal volume may also be affected.[48] Many factors have been identified that increase the risk of opiate-related suppression of respiratory drive, including relief of pain itself. Elderly patients and those with COPD, renal impairment, asthma, cor pulmonale, hypoxia, or hypercapnia are particularly susceptible to opiate-induced reduction in respiratory drive, even at therapeutic levels. The sedating effects of opiates are thought to contribute to reduction in respiratory drive; thus addition of antihistamines, benzodiazepines, and other CNS depressants must be performed with caution.[48] While generally perceived in a negative light, the respiratory depressant effects of opiates are useful in the management of dyspnea and air hunger.[48] It is fortunate

that tolerance to the respiratory depressant effects of opioids develops rapidly.[21] Should significant respiratory depression or acute change in mental status occur, naloxone may be initiated. The goal is not to produce normal cognitive function but to titrate to relief of respiratory distress. A solution of 0.04 mg/mL may be prepared by mixing 1 mL of 0.4 mg/mL naloxone with 9 mL of sterile 0.9% sodium chloride. One or 2 mL of the resultant solution is bolused intravenously every 30–60 s until symptoms improve. If the patient does not improve within 10 min or with total naloxone dose of 1 mg, consider other etiologies for change in mental status.[22] The plasma half-life of naloxone is brief, only 30–60 min, so re-emergence may occur, requiring repeat administration of naloxone. Naloxone may be administered intramuscularly or subcutaneously, but onset of action will be delayed. If the patient is on a long-acting opiate, a naloxone drip should be considered.[79] Patients must be monitored for signs of opiate withdrawal.

4.4.6. Sedation

As with the respiratory depressant effects, tolerance to the sedative effects of opiates generally develops over a few days.[48] Sedation is therefore generally more prominent at initiation of opiate therapy or during opiate rotation; if sedation develops and persists longer than 1 week after initiation or rotation, other causes should be ruled out.[22] Reduction of sedation with continued pain relief is best managed by reducing both the dose and frequency of opiate administration to reduce high peak opiate blood levels.[21,22] Alternatively, the dose of opiate may be reduced either by downward dosage titration or by addition of an adjuvant pain management agent.[22] Pharmacologic measures for management of sedation include addition of CNS stimulants dosed in the morning and early afternoon to prevent nighttime insomnia. Caffeine (100–200 mg PO every 6 h), dextroamphetamine (5–10 up to three times daily), methylphenidate (5–10 mg up to three times daily), or modafinil (100–200 mg/day) may offer relief from sedation. If sedation persists despite the above interventions, neuraxial analgesia and/or interventional measures may be required.[22]

4.4.7. Allergy

Careful evaluation of a patient-reported “allergy” to opiates is required, because many patients do not differentiate adverse effects from allergic hypersensitivities. True allergies to opioids are most common with the natural phenanthrene derivatives codeine and morphine.[76] If a patient suffers wheezing, edema, and hives after a dose of opiate, use of an agent from a different structural class is unlikely to be problematic. The phenathrene class includes morphine, buprenorphine, codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. If the allergic reaction was provoked by codeine or morphine, switching to one of the other agents in this class may not provoke the reaction, but close observation is warranted during the initial exposure. The morphinan series is comprised of levorphanol, nalbuphine, and butorphanol. The phenylpiperidine class contains meperidine, fentanyl, sufentanil, and remifentanil, while the diphenylheptane class contains hydromorphone.[48] As mentioned earlier, opiates, the phenanthrene family in particular, may cause degranulation of the mast cell. Response to histamine may mimic a true hypersensitivity. Switching to an agent from another structural family will nonetheless prevent this pseudoallergic reaction.

4.4.8. Myoclonus

Myoclonus (uncontrollable jerking of the extremities or diaphragmatic spasm leading to hiccoughs) is a dose-related side effect of opioids that is thought to stem either from diminished inhibitory effects of glycine in the dorsal horn, from activation of glutamate NMDA receptors, or via inhibition of dopamine signaling in the basal ganglia.[80,81] Myoclonus is generally managed through opioid rotation or through addition of a low-dose benzodiazepine[80] (e.g., clonazepam 0.5 mg orally every 6 h as needed).

4.4.9. Hyperalgesia and allodynia

As discussed in the Pain sensitization section, opioids may induce a paradoxical increase in sensitivity to painful stimuli (hyperalgesia) and/or may cause pain when exposed to stimuli that are not usually painful (allodynia). Opioid-induced pain sensitization (also known as opioid-induced hyperalgesia or OIH) should be suspected when, especially in the absence of disease progression, the patient reports diffuse pain unrelated to the original pain or an increased level of pain with an increasing dosage of medication.[19] It is important to differentiate between OIH and the expected tolerance that may occur with repeated opioid exposure, though both may be simultaneously present.[20] Tolerance occurs due to desensitization of the pain-relieving mechanisms, while hyperalgesia results from sensitization of these mechanisms[20] after the patient has already developed tolerance to opioids.[82] A patient with pure tolerance will require larger doses of opiate to obtain pain relief; these doses will relieve the pain rather than increase pain, as is the case with OIH.[20] In palliative medicine, the clinician must be aware of opiate hyperalgesia when ordering opiates to treat moaning associated with delirium at the end of life.

A trial of opioid rotation,[15,82] addition of an adjunctive pain medication, behavioral management, or interventional pain management may alleviate tolerance or obviate the need for opiate therapy altogether.[82] As previously mentioned, NSAIDs may help alleviate peripheral OIH. If these options are unsuccessful or are not feasible, evaluating the patient after an increase or decrease of opiate dose may help distinguish tolerance from hyperalgesia, bearing in mind that pain will escalate when the patient is suffering from opiate withdrawal.[82] Utilization of opiates that possess kappa antagonism and pharmacologic agents that target the suspected neurobiological origins of hyperalgesia may provide relief.

Buprenorphine is an opiate with weak κ and δ receptor antagonist actions[62,83] and partial μ receptor agonist actions. A rotation to buprenorphine has been shown to produce sustained antihyperalgesic effects and to provide a sustained reduction in subsequent opiate requirements.[82] It is not generally recommended as a first-line agent for the treatment of cancer pain, because it has an upward dosage ceiling.[84]

Methadone is a full μ opiate receptor agonist and glutamate NMDA receptor antagonist.[15,82] Despite difficulties that arise from its unique toxicological and pharmacokinetic properties, methadone has demonstrated benefit in the reduction of high-dose, opiate-induced hyperalgesia.[19] The cough-suppressant dextromethorphan is a non-competitive NMDA receptor antagonist with preliminary evidence to suggest utility in the prevention of OIH.[15,19] Likewise evidence suggests that the NMDA-receptor-antagonist ketamine, an agent approved by the USFDA for induction and maintenance of anesthesia, shows promise in the management of OIH.[15–19] For now, the best approach to patients with suspected OIH is opiate rotation and/or referral to a pain specialist.

4.4.10. Tolerance

Use of opioids over time will lead to tolerance. Escalation of the dose will alleviate pain that emerges due to tolerance. Fortunately, cross-tolerance between opiates is generally not 100%, so opiate rotation (also known as opiate switching) is a useful tool to restore antinociception while simultaneously sparing the opiate dose.[49,68,85]

4.4.11. Maintaining pain control in the opiate-tolerant patient: opiate dose interconversion for opioid rotation

Equianalgesic dosing refers to the dose of one opiate that provides the same level of relief as a second opiate or the dose given by one route of administration (e.g., oral) that is required to provide the same amount of active drug compared to another route (e.g., intravenous). Table 4 displays equianalgesic doses of step 3 opiates, while Table 5 details conversion to and from transdermal fentanyl. These doses were derived from single-dose trials compared with morphine[22,85]; therefore considerable caution is required, especially in cases where drug accumulation may occur, and it may take 5 or more days before the conversion is complete.[84,85]

Table 5
Dose conversions for fentanyl patches.[22,84,86,88]

24 h transdermal fentanyl dose	24-hour morphine equivalents		Oral morphine equivalent dose for breakthrough (mg)
	Oral morphine (mg)	Parenteral morphine (mg)	
25 mcg/24 h	60–134	10–22	10
50 mcg/24 h	135–224	23–37	20
75 mcg/ 24 h	225–314	38–52	30
100 mcg/24 h	315–404	53–67	40

- For larger doses of fentanyl, multiple patches may be required.
- Fentanyl patches should not be cut. While some transdermal fentanyl products are formulated as drug-in-adhesive (as opposed to drug reservoir), studies have not been performed to support cutting or alteration of patches.
- After application of fentanyl patch, a depot of drug is formed in subcutaneous tissues. Thus, when converting from another opioid to fentanyl, doses of short-acting opioid should be provided to cover breakthrough pain. Likewise, when discontinuing fentanyl patches, one must account for continued release of fentanyl from the subcutaneous depot. Generally, one-half of the fentanyl depot will be eliminated over 17 h. The table below offers suggested management strategies during the initial conversion period.
- Patients should be observed closely during the interconversion; the table above is conservative in dosing estimate when converting TO transdermal fentanyl; breakthrough pain may occur. Conversely, when converting FROM transdermal fentanyl, patients should be observed closely for signs of opioid toxicity.

Converting to transermal fentanyl	0 h	4 h	8 h	12 h
From subcutaneous dosing regimen	Apply patch, give full injectable dose	Give 66% of parenteral dose	Give 33% of parenteral dose	Stop parenteral
From IR oral	Apply patch, give full IR dose	Full IR dose	Full IR dose	
From SR oral	Apply patch, give SR dose			
Converting from transermal fentanyl	0 h	4 h	8 h	12 h
To subcutaneous regimen	Remove patch	25% anticipated maintenance dose	50% anticipated maintenance dose	Full dose
To SR oral	Remove patch		Give SR dose	

IR, immediate release; SR, sustained or extended release.

Individual responses are quite variable, so equianalgesic tables must be considered with great caution. Additionally, there is little evidence to support that the dosage conversions work bidirectionally (i.e., a conversion factor for converting from morphine to drug X may not be equivalent when converting from drug X to morphine). During any opiate adjustment or conversion, patients should be monitored closely during the adjustment period.

The general process for calculating dose equivalencies is consistent among potent step 3 opiates, except for conversions involving methadone or transdermal fentanyl; these two conversions are discussed separately.

4.4.12. Switching routes of administration for same opiate

Many opiates undergo extensive first-pass metabolism when administered by the oral route, so parenteral doses are much smaller compared to oral equivalents. When converting between routes, the total daily dose of opiate is calculated by adding all doses taken in the last 24 h. The total daily dose is then multiplied by the ratio of the dose for the desired route to the current route. If the patient's pain was not well controlled on the previous dose, the new total daily dose may be increased by approximately 25%.[84] The new total daily dose is then divided by the appropriate number of daily doses based upon pharmacokinetic profile of the new dosage form (or by 24 h for continuous hourly infusion rate). If converting to a long-acting (ER/LA) formulation, approximately 10% of the total daily dose should be offered in a prompt-release

formulation every 1–2 h as needed for breakthrough pain.[21,22,68,84,85] It is not appropriate to administer long-acting (ER/LA) products on an as-needed basis. The total daily and breakthrough doses are then titrated upward or downward, depending upon patient response (see section above titled Initiation and titration of opiates). Intramuscular administration of parenteral opioids is not recommended.[84]

4.4.13. Switching opiate medications

The total daily dose of opiate is calculated by adding all doses taken in the last 24 h. The total daily dose is then multiplied by the ratio of the new drug dose equivalent to the current drug (see Table 4). This total daily dose is then reduced by 10–50% to allow for incomplete cross-tolerance.[21,68,84,85] The reduced total daily dose is then divided by the appropriate number of daily doses based upon the pharmacokinetic profile of the new drug. If converting to an ER/LA formulation, approximately 10% of the total daily dose should be offered in a prompt-release formulation every 1–2 h as needed for breakthrough pain.[21,22,68,84,85] It is not appropriate to administer long-acting (ER/LA) products on an as-needed basis. The total daily and breakthrough doses are then titrated upward or downward, depending upon patient response (see section above titled Initiation and titration of opiates).

4.4.14. Transdermal fentanyl

Transdermal fentanyl patches are designed to release a drug over a 72-hour period, though significant inter-patient variability exists with regard to drug delivery rates.[84] Transdermal fentanyl is not indicated for opiate-naïve patients, those with acute pain, or patients with unstable poorly managed pain.[86] A 1:1 ratio has been recommended when converting between transdermal and intravenous fentanyl.[84,87] Interconversion between transdermal fentanyl and other opiates is complicated by the delay in onset when initiating fentanyl patches (approximately 12 h post application)[84] and delays in wearing off post-patch removal (17 h to reduce blood level by 50%).[86] Table 5 details conversion to and from fentanyl patches, including recommendations for managing pain during initiation of transdermal fentanyl. Fever, topical application of heat, and excessive exertion may increase the rate of absorption of fentanyl from the transdermal patch and are therefore relative contraindications to use of the patch.[22]

4.4.15. Methadone

Methadone is a racemic mixture of D- and L-isomers. The L-isomer is an inherently long-acting full opiate receptor agonist, while the D-isomer possesses glutamate NMDA receptor antagonist activity and monoamine-reuptake inhibiting actions.[28,50,54,88] The unique pharmacokinetic characteristics of methadone lead to rapid absorption by oral and rectal routes, with an oral bioavailability that averages 80%, but also lead to an unpredictable elimination half-life.[84] Methadone is extensively metabolized hepatically; the primary pathway is catalyzed by the cytochrome oxidase P450 3A4 isoenzyme. It has no known active metabolites, which makes methadone a very attractive agent for use in patients with significant impairment of renal function.[84] Additionally, methadone may prolong the QTc interval, which can precipitate Torsades de Pointes in susceptible patients. It is therefore prudent to avoid use of methadone concomitantly with other known QT-prolonging drugs and to avoid drugs that inhibit the cytochrome oxidase P450 3A4 isoenzyme, when using methadone in patients with underlying cardiac disease, or when using doses of methadone that exceed 100 mg/day, it is prudent to rectify electrolyte abnormalities and perform electrocardiographic monitoring[22,84] and to discontinue or reduce dose of methadone if the QTc interval exceeds 450 ms.[22]

Because of its complicated pharmacokinetic profile and its toxicity profile, use of methadone should be limited to practitioners experienced with the drug.[22,88] Additionally, the ratio of total daily morphine equivalents to equivalent total daily dose of methadone increases with increasing doses of morphine equivalents; in other words, methadone has a greater relative potency as the patient's morphine dose increases. There are several different methods used to interconvert other opiates to methadone. There are two approaches to conversion to

methadone: one advocates a rapid initiation of methadone with discontinuation of the previous opiate, and the other a gradual addition of methadone with simultaneous reduction in the other opiate. A recent systematic review found no superiority of one method over another.[88]

One gradual start method performs the conversion over 3–5 days to reduce the risk of overdosing. In this method, the ratio of morphine to methadone is initially set at 10 mg morphine: 1 mg methadone[84] to calculate the target total daily dose of methadone. On day one, the morphine dose is reduced by approximately one-third, and the methadone is initiated at approximately one-third of the target dose, divided every 8 h; rescue doses of morphine are continued. On day two, if the patient is not exhibiting signs or symptoms of opiate overload, the morphine dose is dropped by another third and the methadone dose increased by one-third, still divided every 8 h, with continued morphine breakthrough coverage. On day three, if the patient lacks adequate pain control, even if the patient is somnolent, the methadone dose is increased by one-third and the morphine is discontinued. A rescue dose of methadone or short-acting opiate is calculated at a dose equivalent to 5–15% of the total daily dose. If the patient has good pain control with significant somnolence, the dose may be maintained at the day-two level or decreased, with discontinuation of morphine and addition of breakthrough coverage calculated at a dose equivalent to 5–15% of the total daily methadone dose.[84] For most patients after initiation, the scheduled methadone dose may be divided every 12 h.[88]

4.5. Adjuvant agents for pain management

Rational polypharmacy, also referred to as combination pharmacotherapy, involves the concept of systematically selecting and integrating pharmacologic agents to provide a synergistic effect in the management of pain.[89] Appropriate selection and integration of medications may address specific pain etiologies, thereby improving pain management while sparing opioid dosing to subsequently reduce opioid side effects, tolerance, and development of hyperalgesia. In order to safely and effectively perform this integration, thorough patient assessment, clear delineation of goals of therapy, and an in-depth understanding of each medication's mechanism of action, side-effect profile, and potential for clinically relevant drug interactions are required.[22,53,90] Generally, due to multiple factors such as cost, risk, and inconvenience, adjuvant agents (other than NSAIDs in WHO step 1) should not be added to opiate regimens simply to reduce opioid doses in functional patients with well-controlled pain.[90] Table 6 matches commonly used adjuvant agents to the particular type or etiology of pain managed.

4.5.1. Alpha-2 adrenergic agonists

Agents that act as agonists on alpha-2 receptor subtypes produce spinal antinociceptive effects by activating this Gi-coupled receptor.[90] Alpha-2 adrenergic agonists, clonidine and tizanidine, have a known spinal antinociceptive effect.[91] Clonidine can be given orally, transdermally, or intraspinally. Intraspinal administration has proven to provide the most benefit in pain management. It specifically targets and reduces neuropathic pain. This drug produces a synergistic analgesic effect with opioids.

Clonidine may produce significant hypotensive effects but significantly potentiates the antinociceptive effects of opiates. Tizanidine is a shorter-acting agent with less hypotensive potential; it is frequently used in the management of spasticity but may hold promise for treatment of various pain disorders.[92]

4.5.2. Anticonvulsants

Neuropathic pain can also be treated with anticonvulsant drugs, such as gabapentin and pregabalin (gabapentinoids). It is thought that these drugs work well as adjuvant analgesics because epilepsy and neuropathic pain share commonalities in their pathophysiology. Both conditions are characterized by neuronal hyperexcitability. Anticonvulsants may relieve lancinating or stabbing pain from neuropathic causes by suppressing action potential generation

Table 6
Adjuvants for pain management.[22,35,84,90,91,97,99]

Class of drug	Type of pain	Drugs and doses	Comments
Alpha-2 adrenergic agonists	Pain	*Clonidine*	Risk of hypotension
	Pain with spasticity	0.1–0.3 mg PO bid	Evidence limited
		Tizanidine	
		8 mg PO up to tid	
Anticonvulsant	Neuropathic	*Carbamazepine*	Drug interactions
		100–400 mg PO tid	
		Clonazepam	
		0.5–4 mg PO bid	
		Gabapentin	Reduce dose in renal impairment
		100–1200 mg PO tid	
		Lamotrigine	
		25–100 mg PO bid	
		Pregabalin	Titrate upward; reduce dose in renal impairment
		75–300 mg PO bid	
Antidepressant and non-tricyclic	Neuropathic	*Bupropion*	Risk of seizures
		100–450 mg PO daily	
		Duloxetine	Hepatotoxicity, do not combine with tamoxifen
		20–30 mg PO bid	
		Venlafaxine	
		50–225 mg PO daily	
Antidepressant and tricyclic	Neuropathic	*Amitriptyline*	Anticholinergic; caution in xerostomia; may cause constipation (amitriptyline, nortriptyline > desipramine)
		10–25 mg PO daily	
		Desipramine	
		10–150 mg every day	
		Nortriptyline	
		10–100 mg daily	
Bisphosphonate	Bone pain	*Zoledronic acid*	Osteonecrosis of jaw
		4 mg IV every 3–4 weeks	
Calcitonin	Bone pain	*Calcitonin*	Limited evidence of efficacy
		100–200 units daily (subcutaneous or intranasal)	
Corticosteroid	Bone pain, increased intracranial pressure and nerve compression	*Dexamethasone*	Minimal mineralocorticoid effects
		4–16 mg/day single or divided doses	
Topical agent	Neuropathic	*Lidocaine patch*	Minimal systemic absorption
		12 h on, 12 h off	

in hyperexcitable neurons. The calcium channel α2-b ligands gabapentin and pregabalin are two anticonvulsants often considered first-line for neuropathic pain.[90,92] Gabapentin is a relatively inexpensive agent that undergoes extensive renal clearance and therefore does not pose a significant risk for drug interactions but does require dosage adjustment in patients with renal impairment. Pregabalin is a controlled substance in DEA schedule 4. It is a bit more costly than gabapentin but like gabapentin poses little risk of drug interactions and requires downward dose adjustment in patients with renal impairment. Both agents are approved by the USFDA for use in the treatment of neuropathic pain. Side effects are similar for both agents: sedation, somnolence, dizziness, fatigue, and edema. Pregabalin may also cause weight gain.[90] A recent randomized double-blind, placebo-controlled study demonstrated that pregabalin was superior to gabapentin, amitriptyline, and opiate monotherapy at controlling neuropathic cancer pain and that gabapentin was superior to amitriptyline and opiate monotherapy.[93]

Carbamazepine has a long history of use and efficacy in the treatment of trigeminal neuralgia. Its use is limited by drug interactions, side effects, and monitoring requirements. Oxcarbazepine is a structural analog of carbamazepine with somewhat lower risk of drug interactions and side effects. Both agents provide multiple mechanisms of action, including blockade of sodium and possibly α2-b calcium channels[90,9] and potassium channels.[95] Carbamazepine is approved by the USFDA in the treatment of trigeminal neuralgia. Side effects for both agents include diplopia, hyponatremia, hepatotoxicity, aplastic anemia, agranulocytosis, Stevens–Johnson syndrome, and other serious hypersensitivity reactions.[9]

Lamotrigine and topiramate are not approved by the USFDA for use in the management of neuropathic pain, but some efficacy in neuropathic pain syndromes has been demonstrated.[95] Lamotrigine prevents the activation of voltage-gated sodium channels and inhibits presynaptic release of glutamate.[94,95] Adverse effects include Stevens–Johnson syndrome (rare), dizziness, headache, nausea, and diplopia[32,94,95] Topiramate reduces activity of voltage-gated sodium channels, activates potassium channels, enhances postsynaptic $GABA_A$ actions, inhibits carbonic anhydrase, and limits activation of glutamate AMPA receptors.[9] Common adverse effects include sedation, increased intraocular pressure, fatigue, weight loss, renal calculi, and nervousness.[32,9]

4.5.3. *Antidepressants*

Serotonin–norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) have demonstrated efficacy for most neuropathic conditions.[90] Tricyclic antidepressants possess multiple mechanisms of action. Tertiary amines such as amitriptyline and imipramine block the reuptake of serotonin, while secondary amines [including the metabolites of amitriptyline (nortriptyline) and imipramine (desipramine)] selectively block the reuptake of norepinephrine. Additionally, these drugs possess antihistaminic effects at the H1 receptor, antagonism of the serotonin 5HT2 receptor subtype, antagonism of the adrenergic α1 receptor subtype, antagonism at muscarinic receptors, and blockade of voltage-gated sodium channels.[96] Adverse effects of the tricyclic antidepressants are myriad: sedation, proarrhythmia, xerostomia, urinary retention, constipation, weight gain, orthostatic hypotension, and tachycardia. Some tolerance to the antimuscarinic effects may develop. Sedation from tricyclic antidepressants may be of benefit for patients with concomitant insomnia.[92] Cyclobenzaprine, a centrally acting muscle relaxant that is structurally related to the tricyclic antidepressants, may provide some relief for pain related to fibromyalgia[32] but with the same side effect risks as seen with the TCA.

Duloxetine and venlafaxine are serotonin–norepinephrine reuptake inhibitors that lack many of the TCA side effects, because they do not directly interact to any great extent with adrenergic, histaminic, or serotonergic receptors nor do they block sodium channels. Duloxetine is approved by the USFDA in the treatment of neuropathic pain and fibromyalgia. Side effects for these drugs include dry mouth, constipation, dizziness, headache, hypertension, and hepatotoxicity.[32,96] Neither the TCA nor the SNRI should be used in combination with tramadol[92] or tapentadol[48] due to the risk for serotonin syndrome. Rapid discontinuation of venlafaxine may precipitate a withdrawal syndrome.[92] Duloxetine should not be used in combination with tamoxifen due to its ability to inhibit activation of tamoxifen via cytochrome oxidase P450 2D6.[97]

4.5.4. Bisphophonates

Metastatic bone pain that does not respond to analgesia is generally treated in a multimodal fashion (e.g., radioablation).[98] In addition to analgesia and multimodal approaches, bisphosphonate drugs may offer some relief.[73] After treating any underlying condition that is deemed to be an oncologic emergency, bisphosphonates may provide some relief of diffuse bone pain by inhibiting osteoclastic activity and stimulating osteoblastic activity.[22] In particular, nitrogen-containing drugs (e.g., zoledronic acid and pamidronate) appear to be more effective than their carbon-containing counterparts.[98,99] Side effects associated with the bisphosphonates include osteonecrosis of the jaw, especially in patients with poor oral hygiene due to prolonged duration of bisphosphonate therapy or a history of multiple myeloma or bone metastases from breast, prostate, or lung cancers.[90]

4.5.5. Calcitonin

Calcitonin has been shown to relieve pain associated with osteoporosis.[100] There is some limited evidence that this efficacy may translate into relief from metastatic bone pain, but the onset of relief is somewhat delayed.[35,73,101]

4.5.6. Corticosteroids

Glucocoticosteroids produce myriad effects to improve comfort in palliative care, including relief of pain. Glucocorticosteroids are particularly effective for bone pain,[73,101] inflammatory pain,[32] and pain caused by capsular stretching.[101] Additionally, corticosteroids may increase feelings of well-being, stimulate appetite, and decrease nausea and vomiting.[73] Side effects associated with short-term use include altered mental status,[68] hyperglycemia, edema, dyspepsia, increased risk of gastrointestinal bleeding, and increased risk of infection, including candidiasis.[90] Long-term use of glucocorticosteroids is generally not indicated.

4.5.7. Topical analgesics

Lidocaine patches have been demonstrated to provide superior relief compared to placebo for peripheral neuropathic pain when applied directly onto the painful area.[92] Lidocaine acts on activated sodium channels to reduce neuronal activity.[5]

Capsaicin first stimulates then desensitizes the transient receptor potential vanilloid (TRPV1) receptor on C-fiber sensory neurons and depletes substance P. It is used off-label for postherpetic neuropathy and diabetic peripheral neuropathy.[35,102] It is generally considered third line for neuropathic pains but, like topical lidocaine, produces minimal systemic exposure from local topical application.[32]

5. Palliative sedation

In the hospice and palliative care patient who cannot be controlled with the above mentioned medications, palliative sedation can be a last option. This should be used only when multi-disciplinary therapies have been used to their fullest and when there is still severe symptomatology. The goal of therapeutic sedation is the relief of severe unendurable symptoms and not to hasten the end of life. There are many drugs that can be chosen for palliative sedation. Benzodiazepines such as midazolam and alprazolam are commonly used. Other choices are phenobarbital, propofol, and thiopental. Usual routes of infusion are intravenous and subcutaneous. Patients may require different levels of sedation in order to get relief from their symptoms. Palliative sedation may decrease the demand for physician-assisted suicide.[103]

References

1. Urch KC. Cancer pain. In: Walsh D, Caraceni A, Fainsinger R, et al., eds. *Palliative Medicine*. 1st ed. Philadelphia, PA: Saunders; 2009:1378–1384.

2. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med*. 2010;16(11): 1248–1257. http://dx.doi.org/10.1038/nm.2235.
3. Kuner R. Central mechanisms of pathological pain. *Nat Med*. 2010;16(11):1258–1266. http://dx.doi.org/10.1038/nm.2231.
4. Milligan ED, Watkins LR. Pathologic and protective roles of glia in chronic pain. *Nat Rev Neurosci*. 2009;10(1): 23–36. doi:10.10358/nm2533.
5. Griffin RS, Woolf CJ. Pharmacology of analgesia. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW, eds. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:264–283.
6. North RA. Molecular physiology of P2X receptors. *Physiol Rev*. 2002;82(4):1013–1067.
7. Charignon D, Späth P, Martin L, Drouet C. Icatibant, the bradykinin B2 receptor antagonist with target to the interconnected kinin systems. *Expert Opin Pharmcother*. 2012;13(15):2233–2247. http://dx.doi.org/1.1517/14656566.2012.723692.
8. Jaggi AS, Singh N. Therapeutic targets for the management of peripheral nerve injury-induced neuropathic pain. *CNS Neurol Disord Drug Targets*. 2011;10(5):589–609.
9. Barth M, Bondoux M, Luccarini J, et al. From bradykinin B2 receptor antagonists to orally active and selective bradykinin B1 receptor antagonists. *J Med Chem*. 2012;55(6):2574–2584. http://dx.doi.org/10.1021/jm2016057.
10. Ruscheweyh R, Wilder-Smith O, Drdla R, Liu XG, Sandkühler J. Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. *Mol Pain*. 2011;7:20. http://dx.doi.org/10.1186/1744-8069-7-20.
11. Woolf CJ, American College of PhysiciansAmerican Physiological Society, Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med*. 2004;140(6):441–451.
12. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemothreapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacol Ther*. 2011;90(3):377–387. http://dx.doi.org/10.1038/clpt.2011.115.
13. Zeilhofer HU, Zeilhofer UB. Spinal dis-inhibition in inflammatory pain. *Neurosci Lett*. 2008;437(3): 170–174. http://dx.doi.org/10.1016/j.neulet.2008.03.056.
14. Zeilhofer HU, Wildner H, Yévenes GE. Fast synaptic inhibition in spinal sensory processing and pain control. *Physiol Rev*. 2012;92(1):193–235. http://dx.doi.org/10.1152/physrev.00043.2010.
15. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract Res Clin Anaesthesiol*. 2007;21(1):65–83. http://dx.doi.org/10.1016/j.bpa.2006.12.004.
16. Kohno T, Ji RR, Ito N, et al. Peripiheral axonal injury results in reduced mu opioid receptor pre- and post-synaptic action in the spinal cord. *Pain*. 2005;117(1-2):77–87.
17. Tsuzuki K, Kondo E, Fukuoka T, et al. Differential regulation of P2X(3) mRNA expression by peripheral nerve injury in intact and injured neurons in the rat sensory ganglia. *Pain*. 2001;91(3):351–360.
18. De Kock MF, Lavand'homme PM. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. *Best Pract Res Clin Anaesthesiol*. 2007;21(1):85–98.
19. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145–161.
20. Ramasubbu C, Gupta A. Pharmacological treatment of opioid-induced hyperalgesia: a review of the evidence. *J Pain Palliat Care Pharmacother*. 2011;25(3):219–230. http://dx.doi.org/10.3109/15360288.2011.589490.
21. Miaskowski C, Cleary J, Burney R, et al. *Guideline for the Management of Cancer Pain in Adults and Children*. Glenview, IL: American Pain Society (APS); 2005.
22. *National Comprehensive Cancer Network (NCCN)*. Oncology: palliative care. Ver 2. 2012. ⟨http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf⟩; Accessed 09.15.12.
23. Jost L, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical recommendations. *Ann Onc*. 2007;18(suppl 2):ii92–ii94.
24. Kvale PA, Selecky PA, Prakash UB, American College of Chest Physicians. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). *Chest*. 2007;132(suppl 3):368S–403S. http://dx.doi.org/10.1378/chest.07-0994.
25. *National Institute for Health and Clinical Excellence (NICE)*. Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults. NICE Clinical Guideline (CG) 140. ⟨http://publications.nice.org.uk/opioids-in-palliative-care-safe-and-effective-prescribing-of-strong-opioids-for-pain-in-palliative-cg140⟩; 2012 Accessed 02.01.13.
26. World Health Organization. *Cancer Pain Relief with a Guide to Opioid Availability*. 2nd ed. Geneva, Switzerland: WHO; 1996.
27. McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. NSAIDs or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev*. 2005(1):CD005180.
28. Reville B, Axelrod D, Maury R. Palliative care for the cancer patient. *Prim Care*. 2009;36(4): 781–810. http://dx.doi.org/10.1016/j.pop.2009.07.010.
29. Axelsson B, Borup S. Is there an additive analgesic effect of paracetamol at step 3? A double-blind randomized controlled study. *Palliat Med*. 2003;17(8):724–725.
30. Israel FJ, Parker G, Charles M, Reymond L. Lack of benefit from paracetamol (acetaminophen) for palliative cancer patients requiring high-dose strong opioids: a randomized, double-blind, placebo-controlled, crossover trial. *J Pain Symptom Manage*. 2010;39(3):548–554.
31. Nabal M, Librada S, Redondo MJ, Pigni A, Brunelli C, Caraceni A. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer: a systematic review of the literature. *Palliat Med*. 2012;26(4):305–312.
32. *U.S. Food and Drug Administration*. Acetaminophen information. ⟨http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm⟩; Accessed 02.01.13.
33. Hooten WM, Timming R, Saeger L, et al. Health care guideline: assessment and management of chronic pain. 5th ed. Bloomington, MN: Institute for Clinical Systems Improvement; 2011 Accessed 02.01.13.

34. Buvanendran A, Lipman AG. Nonsteroidal anti-inflammatory drugs and acetaminophen. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. *Bonica's Management of Pain*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1157–1171.
35. Fine PG, Miaskowski C, Paice JA. Meeting the challenges in cancer pain management. *J Support Oncol*. 2004;2(6 suppl 4):5–22. [quiz 23-24].
36. Grosser T, Smyth EM, FitzGerald GA. Anti-inflammatory, antipyretic, and analgesic agents; pharmacotherapy of gout. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:959–1004.
37. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001;345(6):433–442.
38. Furst DE, Ulrich RW, Prakash S. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics, & drugs used in gout. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York: McGraw-Hill; 2012:635–658.
39. Andrade C, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71(12):1565–1575.
40. Abuelo JG. Normotensive ischemic acute renal failure. *N Engl J Med*. 2007;357(8):797–805.
41. Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation*. 2006;114(10):1028–1035.
42. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352(11):1092–1102.
43. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J Clin Invest*. 2006;116(1):4–15.
44. Reddy SK, Lopez G, Elsayem A. Pain management and symptom control. In: Kantarjian HM, Wolff RA, Koller CA, eds. *The MD Anderson Manual of Medical Oncology*. 2nd ed. New York: McGraw-Hill; 2011.
45. Prommer EE. Tramadol: does it have a role in cancer pain management? *J Opioid Manag*. 2005;1(3):131–138.
46. Pergolizzi JV Jr, Mercadante S, Echaburu AV, et al. The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel concensus. *Curr Med Res Opin*. 2009;25(6):1517–1528.
47. Max MB, Payne R, Edwards WT, et al. The American Pain Society: Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. Glenview, IL: American Pain Society; 2003.
48. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:481–526.
49. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13:e58–e68. http://dx.doi.org/10.1016/S1470-2045(12)70040-2.
50. Nauck F, Hardy JR. Opioids. In: Walsh D, Caraceni A, Fainsinger R, et al., eds. *Palliative Medicine*. 1st ed. Philadelphia, PA: Saunders; 2009:754–759.
51. *Scottish Intercollegiate Guidelines Network (SIGN)*. Control of pain in adults with cancer: a national clinical guideline. Edinburgh, Scotland: SIGN; 2008. ⟨http://www.sign.ac.uk/pdf/sign106.pdf⟩; Accessed 02.06.13.
52. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain*. 2002;18(suppl 4):S3–S13.
53. Quigley C. Opioids in people with cancer-related pain. Clin Evid. 2008. ⟨http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907984/⟩; Accessed 02.06.13. Doi:pii:2408.
54. Bryson J, Tamber A, Seccareccia D, Zimmermann C. Methadone for treatment of cancer pain. *Curr Oncol Rep*. 2006;8(4):282–288.
55. *Department of Veterans Affairs (VA), National VA Pain Outcomes Working Group, National VA Pain Management Coordinating Committee*. VHA (Veterans Health Administration) pain outcomes toolkit. United States Department of Veterans Affairs Web site. ⟨http://www.va.gov/PAINMANAGEMENT/docs/Outcomes.doc⟩; 2003 Accessed 02.06.13.
56. Gillis DH. *Federal Register*. 1993;58(1310):37507.
57. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10(2):131–146. http://dx.doi.org/10.1013/j.pain.2008.10.009.
58. Gudin J. Risk evaluation and mitigation strategies (REMS) for extended-release and long-acting opioid analgesics: considerations for palliative care practice. *J Pain Palliat Care Pharmacother*. 2012;26(2):136–143. http://dx.doi.org/10.3109/15360288.2012.679724.
59. *U.S. Food and Drug Administration (USFDA)*. Risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids. ⟨http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm⟩. Accessed 08.30.12. USFDA Web site. 09.06.12. Accessed 02.06.13.
60. Schumacher MA, Basbaum AI, Way WL. Opioid analgesics & antagonists. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York: McGraw-Hill; 2012.
61. Fine P, Portenoy RK. *Opioid Analgesia*. New York: McGraw-Hill; 2004. Accessed 02.06.13.
62. *Mallinckrodt*. Highlights of prescribing information: Exalgo (hydromorphone HCl) extended-release tablets for oral use, CII. Hazelwood, MO: Mallinckrodt. Revised August 2012. ⟨http://www.mallinckrodt.com/WorkArea/DownloadAsset.aspx?id=2147483728⟩; Accessed 02.06.2013.
63. Waller A, Caroline NL. Principles and techniques of pharmacologic management. In: Waller A, Caroline NL, eds. *Handbook of Palliative Care in Cancer*. 2nd ed. Boston, MA: Butterworth-Heinemann; 2000:41–58.
64. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain*. 2003;4(1):2–21.
65. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage*. 2003;25(5):406–411.
66. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88(3):287–294.

67. Jensen MP, Martin SA, Cheung R. The meaning of pain relief in a clinical trial. *J Pain*. 2005;6(6):400–406.
68. *United States Department of Veterans Affairs (VA)*. Management of opioid therapy (OT) for chronic pain. VA/DOD (Department of Defense) clinical practice guidelines. ⟨http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp⟩; Accessed 02.06.2013.
69. McQuaid KR. Drugs used in the treatment of gastrointestinal diseases. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York: McGraw-Hill; 2012:1081–1114.
70. *Salix Pharmaceuticals, Inc*. Highlights of prescribing information: Relistor (methylnaltrexone bromide) subcutaneous injection. Raleigh, NC: Salix Pharmaceuticals, Inc. ⟨http://www.relistor.com/assets/pdf/relistor-methylnaltrexone-bromide-pi.pdf⟩; 2008 Accessed 02.06.2013.
71. Aminoff MJ. Pharmacologic management of parkinsonism & other movement disorders. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 12th ed. New York: McGraw-Hill; 2012:483–500 [Chapter 28].
72. Davis MP, Walsh D. Treatment of nausea and vomiting in advanced cancer. *Support Care Cancer*. 2000;8(6):444–454.
73. Astolfi J. Palliative care. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill; 2011:23–24.
74. Skidgel RA, Kaplan AP, Erdös EG. Histamine, bradykinin, and their antagonists. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:911–936.
75. Sharkey KA, Wallace JL. Treatment of disorders of bowel motility and water flux; anti-emetics; agents used in biliary and pancreatic disease. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:1323–1350.
76. Jellin J, ed. Analgesic options for patients with allergic-type opioids reactions. Pharm Lett. 2006;22. [2202012006].
77. Meyer JM. Pharmacotherapy of psychosis and mania. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:417–456.
78. American Geriatrics Society 2012 Beers Criteria Update Expert Panel Fick D, Semla T, Beizer J, Brandt N, Dombrowski R, et al. American Geriatric Society updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616–631.
79. Doyon S. In: Tintinalli JE, Stapczynski JS, Ma OJ, Cline DM, Cydulka RK, Meckler GD, eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*. 7th ed. New York: McGraw-Hill; 2011.
80. Mercadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. *Pain*. 1998;74(1):5–9.
81. Lauterbach EC. Hiccup and apparent myoclonus after hydrocodone: review of the opiate-related hiccup and myoclonus literature. *Clin Neuropharmacol*. 1999;22(2):87–92.
82. Silverman SM. Opioid induced hyperalgesia: clinical implications for the pain practitioner. *Pain Physician*. 2009;12(3):679–684. Accesssed 02.07.13.
83. Induru RR, Davis MP. Buprenorphine for neuropathic pain—targeting hyperalgesia. *Am J Hosp Palliat Care*. 2009;26(6):470–473. http://dx.doi.org/10.1177/1049909109341868.
84. *National Cancer Institute (NCI) Physician Data Query (PDQ®) Supportive and Palliative Care Editorial Board*. Pharmacologic management. In: National Cancer Institute (NCI) PDQ® Supportive and Palliative Care Editorial Board. PDQ® pain. ⟨http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/page3#Section_165⟩; Accessed 02.07.13.
85. Berdine HJ, Nesbit SA. Equianalgesic dosing of opioids. *J Pain Palliat Care Pharmacother*. 2006;20(4):79–84. http://dx.doi.org/10.1300/J354v20n04_16.
86. *Janssen Pharmaceuticals, Inc*. Duragesic® (fentanyl transdermal system): Highlights of prescribing information. Revised July 2012. ⟨http://www.duragesic.com/sites/default/files/pdf/duragesic_0.pdf⟩; Accessed 02.07.13.
87. Kornick CA, Santiago-Palma J, Schulman G, et al. A safe and effective method for converting patients from transdermal to intravenous fentanyl for the treatment of acute cancer-related pain. *Cancer*. 2003;97(12):3121–3124.
88. Leppert W. The role of methadone in cancer pain treatment—a review. *Int J Clin Pract*. 2009;63(7):1095–1109. http://dx.doi.org/10.1111/j.1742-1241.2008.01990.x. 1095.
89. Zacharoff KL. The role of rational polypharmacy in pain management. PainEDU.org Web site. March 11, 2008. ⟨http://www.painedu.org/articles_timely.asp?ArticleNumber=17⟩; Accessed 02.07.13.
90. Knotkova H, Pappagallo M. Adjuvant analgesics. *Med Clin North Am*. 2007;91(1):113–124.
91. Khan MI, Walsh D, Brito-Dellan N. Opioid and adjuvant analgesics: compared and contrasted. *Am J Hosp Palliat Care*. 2011;28(5):378–383.
92. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237–251.
93. Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Paliat Care*. 2012;29(3):177–182. http://dx.doi.org/10.1177/1049909111412539.
94. McNamara JO. Pharmacotherapy of the epilepsies. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:583–608.
95. Eisenberg E, River Y, Shifrin A, Krivoy N. Antiepileptic drugs in the treatment of neuropathic pain. *Drugs*. 2007;37(9):1265–1289.
96. O'Donnell JM, Shelton RC. Drug therapy of depression and anxiety disorders. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:397–416.
97. Yin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*. 2005;97(1):30–39.
98. Costa L, Major PP. Effect of bisphosphonates on pain and quality of life in patients with bone metastases. *Nat Clin Pract Oncol*. 2009;6(3):163–174.

99. Diel IJ. What do patients with metastatic bone pain need? *Eur J Cancer Suppl*. 2006;4(8):1–3.
100. Chesnut CH 3rd, Azria M, Silverman S, et al. Salmon calcitonin: a review of current and future therapeutic indications. *Osteoporos Int*. 2008;19(4):479–491.
101. Emanuel EJ. Palliative and end-of-life care. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012:67–84 [Chapter 9].
102. Burkhart C, Morrell D, Goldsmith L. Dermatological pharmacology. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011:1803–1832.
103. Carr MF, Mohr GJ. Palliative sedation as part of a continuum of palliative care. *J Palliat Med*. 2008;11(1):76–81.