

Cancer Pain Management: Comprehensive Assessment and Nonopioid Analgesics, Part I

RITA J. WICKHAM, PhD, RN, AOCN®

From Rush University College of Nursing
(Adjunct Faculty), Chicago, Illinois

Author's disclosures of potential conflicts of
interest are found at the end of this article.

Correspondence to: Rita Wickham, PhD, RN,
AOCN®, 8039 Garth Point Lane, Rapid River, MI
49878. E-mail: rita.j.wickham@gmail.com

<https://doi.org/10.6004/jadpro.2017.8.5.4>

© 2017 Harborside Press®

Abstract

Pain is still undertreated and thus a significant problem for at least half of all cancer patients. Inadequately managed cancer pain may cause significant morbidity and even affect mortality, as well as patient quality of life. One enduring problem is suboptimal pain education in basic and advanced educational programs, and many myths and knowledge gaps persist. This article focuses on identifying and dispelling myths, thorough baseline and ongoing pain assessment, pain documentation, and interprofessional collaboration. It includes a comprehensive review of appropriate use of nonopioid analgesics—nonsteroidal anti-inflammatory agents and acetaminophen, and so-called adjuvant analgesics, such as antidepressants, anticonvulsants, and other drugs.

J Adv Pract Oncol 2017;8:475-490

“

**Untreated cancer pain
is a human disaster not
unlike famine; its victims
are starving for relief.”**

Ronald Piana
The New York Times
October 1, 2014

About 50% of cancer patients have undertreated pain, and the percentage is even greater among minority patients (Fisch et al., 2012; Paice & Von Roenn, 2014; Stein, Alcaraz, Kamson, Fallon, & Smith, 2015). Unrelieved pain is not inconsequential and can alter immunity and organ function, increase anxiety and depression, affect well-being and quality of life, and may even hasten death (Glare et al., 2014; Paice, 2010). Educational gaps and other barriers continue to affect interprofessional and oncology advanced practitio-

ners' (APs) roles in pain management for patients undergoing active cancer treatment or receiving palliative or survival care. This article is the first part of a two-part series centering on analgesics and will discuss barriers to cancer pain management, comprehensive assessment, and nonopioid analgesics. The focus of the second part, which will appear in a future issue of *JADPRO*, will be opioid analgesics. Nondrug measures are essential to optimal cancer pain control but are beyond the scope of this series.

There are persistent gaps in pain management content in prelicensure

and postgraduate health-care education (Institute of Medicine, 2011; Duke, Haas, Yarbrough, & Northam, 2013; Hunter et al., 2008; Murinson et al., 2013). Furthermore, professional and patient barriers still impede optimal cancer pain control (Breuer, Fleishman, Cruciani, & Portenoy, 2011; Kwon, 2014; Paice & Ferrell, 2011; Stein et al., 2015; Vallerand, Collins-Bohler, Templin, & Hasenau, 2007). Possible clinician barriers include inadequate knowledge regarding pain management principles, incorrectly held beliefs about adverse effects and addiction, little access to and collaboration with supportive care services, and concerns about legal and regulatory restrictions. Among patients, minority and elderly individuals are more likely to be uncomfortable talking to providers about their pain, to believe pain signals worsening cancer, to believe pain cannot be relieved, to have unaddressed concerns about addiction and side effects, and to be unable to pay for analgesics.

Sociopolitical factors are a recurring barrier, as spotlighted by Von Gunten (2016): "...A common belief among the public, including physicians, is that an opioid like morphine, even if prescribed by a physician for a medical indication, causes addiction" (p 348). The "evidence" for this myth is oft quoted and supported by flawed statistics that mistakenly calculate the rate of addiction as:

$$\frac{\text{Number of opioid addicts first introduced to opioids as prescription drugs}}{\text{All opioid addicts}}$$

This quotient is an erroneously estimated addiction rate of 60% to 100%. The correct calculation is:

$$\frac{\text{All people with pain treated with an opioid who become addicted}}{\text{All people with pain and treated with an opioid}}$$

This quotient reflects the actual iatrogenic risk for addiction or substance abuse of legitimately and appropriately prescribed opioids as 0.01% to 4%.

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), 75% of prescription opioid abusers are taking a family member's or friend's opioids or buying them on the street (Center for Behavioral Health Statistics and Quality, 2015; Cicero, Ellis, Surratt, & Kurtz,

2014). This is particularly salient given the highly publicized recommendations from the Centers for Disease Control (CDC) to limit opioid prescriptions for chronic pain (Dowell, Haegerich, & Chou, 2016). The CDC report explicitly excludes cancer pain, but the surrounding press may reinforce negative (and emotional) misconceptions about using opioid analgesics, even among cancer patients or their families. For instance, the CDC recommendations were followed by the Comprehensive Addiction and Recovery Act (CARA), which has implications for APs and patients (Viale, 2016). In response, the American Society of Clinical Oncology (ASCO) published a policy statement supporting access to opioids for cancer pain (ASCO, 2016).

BASELINE PAIN ASSESSMENT

Oncology clinicians know regular pain assessment and documentation are essential but may not incorporate them into routine practice (Paice & Ferrell, 2011; Wells, McDowell, Hendricks, Deitrich, & Murphy, 2011). Many patients report that clinicians do not even ask about pain. Comprehensive assessment is the foundation for a pain management plan (drug and nondrug), reevaluation, and subsequent modifications in the plan.

Location

As many as 80% of cancer patients have multiple sites of pain; therefore, APs should ask patients to identify all painful sites and determine whether each is localized or spreads (radicular or referred; Caracenia & Portenoy, 1999). It is easier to pinpoint somatic pain (e.g., pathologic fractures), but visceral pain may be vague or referred to overlying skin or a distant site. For example, aching or gnawing right shoulder pain may be referred from hepatomegaly; left back pain may arise from a pancreatic tumor; and diffuse abdominal pain may be caused by omental inflammation, bowel or duct obstruction, hollow viscera stretching, or ascites, ischemia, or hepatomegaly (Shaiova, 2006). About 13% of patients with spinal metastases have radicular pain along affected dermatomes of distorted or compressed nerve roots, and some have accompanying motor or sensory deficits and hyperreflexia (Chang, Janian, Jain, & Chau, 2006). Thus, a metastatic deposit in the right side of the lumbar one vertebra (L1) could cause waist-level back pain ra-

Table 1. Pain Descriptors and Analgesic Selection

Type of pain	Examples	Descriptors	Analgesic agent(s)	
<i>Nociceptive</i>				
Somatic	<ul style="list-style-type: none"> • Pathologic fracture • Mucositis • Bone metastases • Malignant ulcers • Surgical incision 	<ul style="list-style-type: none"> • Aching • Deep • Dull • Gnawing • Piercing • Pounding • Pressing • Pulsing 	<ul style="list-style-type: none"> • Rasping • Sharp • Sore • Taut • Tearing • Tender • Throbbing 	<ul style="list-style-type: none"> • NSAID/acetaminophen • Opioid
Visceral	<ul style="list-style-type: none"> • Partial/complete bowel obstruction • Hepatomegaly (capsular distension) 	<ul style="list-style-type: none"> • Cramping • Deep aching • Dull • Gassy/bloated 	<ul style="list-style-type: none"> • Pressure • Sharp • Squeezing • Tightness 	<ul style="list-style-type: none"> • Opioid • Antispasmodic/antisecretory
<i>Neuropathic</i>				
	<ul style="list-style-type: none"> • Nerve root compression • Phantom limb pain • Plexopathies • Postherpetic neuralgia 	<ul style="list-style-type: none"> • Aching • Boring • Burning • Flickering • Hot or cold • Itchy • Numb • Piercing 	<ul style="list-style-type: none"> • Pinching • Radiating • Shooting • Smarting • Stabbing • Tingling • Touchy 	<ul style="list-style-type: none"> • Adjuvant • Opioid
<i>Evaluative, affective descriptors</i>				
		<ul style="list-style-type: none"> • Aggravating • Annoying • Exhausting • Fearful 	<ul style="list-style-type: none"> • Miserable • Nagging • Sickening • Tiring 	

Note. NSAID = nonsteroidal anti-inflammatory drug. Information from Chang et al. (2006); Dworkin et al. (2007); Epstein, Wilkie, Fischer, Kim, and Villines (2009); Holtan & Kongsgaard (2009); Mackey et al. (2012); Matthie & McMillan (2014); Shaiova (2006).

diating to the right hip and groin. Percussion of involved vertebrae usually elicits pain or tenderness.

Quality

Asking “What does your pain feel like?” elicits details about pain quality that may aid analgesic selection (Table 1). Patients often use more than one quality word, reflecting different pain mechanisms (nociceptive or neuropathic) and analgesic choices (Chang et al., 2006; Dworkin, Jensen, Gammaitoni, Olaleye, & Galer, 2007; Holtan & Kongsgaard, 2009; Mackey et al., 2012; Pasternak, 2014). Visceral pain might be accompanied by nausea and vomiting, anorexia, bloating, and diaphoresis (Matthie & McMillan, 2014; Shaiova, 2006). Patients with neuropathic pain may have paresthesia (numbness or pins and needles), allodynia (pain evoked by a nonpainful stimulus, such as clothing or sheets touching the skin), dysesthe-

sia (unusual or strange sensations described as painful), or autonomic changes (mottled or pink skin) over the painful area (Gilron, Tu, & Holden, 2013; Kerba, Wu, Duan, Hagen, & Bennett, 2010).

Intensity

Numerical rating scales (NRS) such as 0 to 10, and verbal rating scales (VRS) such as none, mild, moderate, or severe, are reliable, valid, and sensitive pain-intensity measures that most people understand easily (Brunelli et al., 2010; Hartrick, Kovan, & Shapiro, 2003; Hjermstad et al., 2011). The Faces Pain Scale–Revised (FPS-R) is similarly psychometrically sound and may be a useful alternative for some patients (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011; Swarm et al., 2010). An initial strategy may be asking a patient to rate pain severity on two scales to help them identify the scale they best understand. The Breakthrough

Pain (BTP) Assessment is a 14-item list specific to BTP (Webber, Davies, & Cowie, 2016).

Temporal Pattern of Pain

Another assessment goal is to clarify temporal aspects: whether pain is constant or intermittent, what *aggravating* or *alleviating factors* increase or decrease pain, or whether pain is *paroxysmal (breakthrough)* or *end-of-dose failure*. Constant pain requires around-the-clock (ATC) analgesics. Up to 66% of cancer patients with well-controlled baseline pain have episodes of severe breakthrough pain—sudden, unpredictable, and spontaneous, or predictable incident pain provoked by specific triggers (e.g., weight bearing, coughing, or wound changes); these pains peak in 3 to 10 minutes and last about 30 minutes (Caraceni, Martini, Zecca, & Portenoy, 2004; Daeninck et al., 2016; Davies et al., 2013; Greco et al., 2011). End-of-dose failure occurs with sustained-release (SR) or transdermal opioids, when pain returns earlier than predicted with *every* dose. For example, a patient taking morphine SR every 12 hours experiences pain 10 hours after every dose (more common with generic SR products) is managed by changing morphine SR to every 8 hours.

Effects of Pain on Mood, Activities, and Sleep

The AP should ask the patient whether pain interferes with any daily activities, roles, work, enjoyment of life, emotional functioning, and sleep (McMillan, Toftagen, & Morgan, 2008; Tavoli, Montazeri, Roshan, Tavoli, & Melyani, 2008; te Boveldt et al., 2013). These interrelated effects are often associated with depression and can occur even with mild pain but are magnified with moderate and severe pain.

Analgesic History

An accurate analgesic history should identify analgesics discontinued because of unmanageable side effects or ineffective analgesia at maximized doses. Reviewing the patient's current analgesics with them confirms doses taken (baseline and as needed [PRN]). For example, if another prescriber instructed the patient with pain to increase baseline or take more frequent PRN doses, the prescriber may not have documented this in the patient's medical record (MR). Other patients do not take prescribed

opioids because of unaddressed concerns or unmanaged adverse effects (Gunnarsdottir, Donovan, Serlin, Voge, & Ward, 2002; Kwon, 2014).

Patient's Goal for Pain Relief

The AP should ask and document the patient's estimate of acceptable pain level/relief (Hui & Bruera, 2014). Most patients state mild pain is tolerable, and few request complete pain relief (Dalal et al., 2012). This is also the time to explore patient beliefs and concerns about pain and analgesia, which may be influenced by culture, religion, adverse effects, worries about addiction, paying for analgesics, or even opioid availability at local pharmacies (Kwon, 2014; Situ, Wang, Shao, & Zhu, 2012).

At reassessment, asking the patient whether current pain control is "good enough" or "could be a little better" aids in tweaking analgesic doses. Another way to determine this is to ask whether their pain is worse, the same, or better than at the last assessment and to quantify this with a relief scale (0% to 100%, or none, slight, moderate, or complete) to evaluate analgesia (Gilron & Jensen, 2011). *Any* improvement helps patients to focus on positive aspects of a management plan and increases their confidence that further pain relief is possible. It may be helpful for the patient to reframe the situation by asking: "What can you do now that you could not do before starting this pain medicine?" Questions about any new and bothersome side effects—the other side of the efficacy coin—are equally important to analgesic planning.

Risk Assessment for Substance Use

Exploring any personal or family history of alcohol or drug use or diagnosed major psychiatric disorder should be routine, as such factors *may* signify increased risks for aberrant drug-taking behaviors (Barclay, Owens, & Blackhall, 2014; Portenoy & Ahmed, 2014). Other clues *might* reflect risk, such as having a cancer associated with heavy alcohol use or smoking (e.g., head and neck cancer), being a current heavy smoker, having a history of automobile accidents or prolonged unemployment, or having a limited support system. Conversely, patients with limited prognoses or those who are in recovery programs are at lower risk. It is critical to ask patients about drug and alcohol use, rather than accepting comments about "drug-seeking behaviors"

and situations and any treatment interventions. Most people will be truthful, but asking exaggerated questions such as, “Do you use recreational heroin?” or “Do you drink two bottles of wine or hard liquor or a case of beer each day?” usually prompts honest answers about less extreme use.

There are no universally accepted definitions of substance abuse (use disorder) and addiction; however, some definitions for substance abuse and addiction, as well as dependence, tolerance, and drug diversion or pseudoaddiction, are summarized in Table 2. The current American Psychiatric Association (APA) diagnostic labels of “substance use disorder” and “addiction” are not interchangeable (APA, 2013; Hartney, 2016). The APA criteria for substance use (e.g., alcohol, cannabis, hallucinogens, inhalants, opioids, anxiolytics, and tobacco) disorders are categorized from mild to severe (Norko & Fitch, 2014). The American Pain Society, the American Society of Addiction Medicine, and the American Academy of Pain Medicine agree that addiction is a complex problem and is not synonymous with dependence and tolerance (American Society of Addiction Medicine, 2011; Heit, 2003; Volkow & McLellan, 2016).

Weissman and Haddox (1989) coined the term “pseudoaddiction” to describe labeling patients as “drug-seekers” or “addicts” because they ask for larger-than-ordered or more frequently-than-prescribed opioid doses when prescriptions are inade-

quate. Clinicians often mistrust “pseudoaddicted” patients, leading to adversarial relationships. On the other hand, a clinician who strongly suspects a patient of diversion (a legal problem) *must* stop prescribing drugs with abuse potential and investigate the situation (Portenoy & Ahmed, 2014).

Dependence and tolerance are physical phenomena but are *not* addiction. Continued opioid occupancy at receptors results in physical dependence, which occurs with steroids and some other drugs. This means withdrawal syndrome (e.g., anxiety, insomnia, agitation, abdominal cramping, etc.) will occur if an opioid antagonist (e.g., naloxone) is administered or an opioid is abruptly stopped rather than titrating doses downward. Tolerance is also physical, whereby adverse effects resolve (tolerance develops) or analgesia declines; this is a rare event in cancer patients, who almost always need larger doses because of increased, tumor-related pain (Ripamonti, Santini, Maranzano, Berti, & Roila, 2012). Unfortunately, the APA substance use criteria include tolerance and withdrawal, and other criteria (using larger amounts for longer periods, attempts to quit or control use) can be subjectively defined in some situations.

Advanced practitioners should explore patient concerns about becoming “hooked” to opioids, having unmanaged side effects, or believing that opioids are a “last resort” or hasten death (Bedard et al., 2013; Gunnarsdottir et al., 2002; Kwon, 2014; Reid,

Table 2. Addiction, Tolerance, Dependence, and Substance Use Disorder (DSM-5)

- **Addiction** is a complex, chronic, relapsing brain disease with genetic, psychosocial, and environmental influences. Characterized by one or more of the “Cs”: (1) impaired *control* of drug use; (2) *compulsive use*; (3) *continued use* despite harm; and (4) *craving*
- **Dependence** is a *physical* state of adaptation (to a drug at a receptor); physical withdrawal (abstinence syndrome) occurs if an antagonist is administered or the drug is stopped suddenly
- **Tolerance** is a *physical* effect by which analgesia or adverse effects diminish over time

DSM-5 Substance Use Disorder (SUD)

- | | |
|--|--|
| <ul style="list-style-type: none"> • Used larger amounts or for longer periods than originally intended • Repeated attempts to quit or control use • Significant time spent getting/using or recovering from substance • Craving • Decreased social, occupational, or recreational activities due to substance use • Continued use despite social or interpersonal problems due to the substance use • Activities given up to use • Continued use despite subsequent physical/psychological problems • Hazardous use • Tolerance • Withdrawal | <p>SUD classification</p> <p>2–3 criteria = mild SUD</p> <p>4–5 criteria = moderate SUD</p> <p>≥ 6 criteria = severe SUD</p> |
|--|--|

Note. Information from American Society of Addiction Medicine (2011); National Institute on Drug Abuse (2016); Norko and Fitch (2014); Hartney (2016); Heit (2003).

Goberman-Hill, & Hank, 2008). There is evidence that *poorly controlled* pain actually shortens life, and taking opioids for cancer pain may *increase* survival (Halabi et al., 2008; Minami, Fujimoto, Ogata, Yamamoto, & Komuta, 2015; Portenoy et al., 2006). Family members may hold similar or more negative beliefs and influence a patient's willingness or ability to take analgesics. Addressing family learning needs and dispelling concerns should thus be part of a pain management plan (Vallerand et al., 2007).

ANALGESICS

The analgesic ladder was intended to address inadequate cancer pain management in underdeveloped countries and guide step-wise analgesics for mild pain—a step 1 nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen (APAP); a step 2 “weak” opioid for moderate pain; or a step 3 “strong” opioid for severe pain—with an adjuvant analgesic, as indicated, at any step (World Health Organization, 1987). Suggested changes include adding new analgesics, a two-step approach with small morphine-like opioid doses for moderate pain, or adding a pain intervention step (Eisenberg, Marinangeli, Birkhahm, Paladín, & Varrassi, 2005; Maltoni et al., 2005; Vargas-Schaffer, 2010). The ladder approach is helpful to frame analgesic “educated guesses” but is not exact as 24% to 30% of patients do not attain “best” pain relief (Stute, Lehmann, & Grond, 2001; Zech, Grond, Lynch, Herte, & Lehmann, 1995).

NONOPIOID ANALGESICS: NSAIDS AND ACETAMINOPHEN

Over-the-counter (OTC) and prescription NSAIDs are useful for mild to moderate pain with an inflammatory component (e.g., bone metastases or fungating lesions). Regularly scheduled NSAIDs should be taken for maximal efficacy, and adding an NSAID to an opioid for severe pain may enhance analgesia and allow lower opioid doses. The NSAIDs interrupt cyclooxygenase (COX) enzyme (COX-1 and COX-2) conversion of arachidonic acid to prostaglandins and thromboxanes, which may modulate, intensify, or maintain pain (Paice & Ferrell, 2011; Pountos, Georgouli, Bird, & Giannoudis, 2011). In addition, COX-1 and COX-2 have important roles in normal organ function and homeostasis (Kirkby et al., 2013).

All NSAIDs except celecoxib are nonselective (Table 3) and bind with varying potencies to COX-1 and COX-2 (Grosser, 2009; James & Cleland, 2006). Aspirin (ASA), the prototypic nonselective NSAID, irreversibly inhibits COX activity for its duration in particular target tissues (Knights, Mangoni, & Miners, 2010; Munir, Enany, & Zhang, 2007). For instance, repeated aspirin doses ≥ 30 mg/day cause cumulative and dose-related platelet inhibition, with recovery 8 to 12 days after aspirin is stopped. Platelet effects from other NSAIDs are reversible, and times to recovery differ.

The NSAIDs (except ketorolac) are relatively inexpensive. The NSAID half-lives vary; a longer half-life means less frequent dosing but may increase the risk for adverse effects, especially in elderly or unhealthy people (Amadio, Cummings, & Amadio, 1993). The NSAIDs have an analgesic ceiling, above which only toxicity increases. A safe strategy is topical NSAID application over a painful site, which may decrease pain with little risk for systemic absorption and adverse effects (Pountos et al., 2011).

Adverse Effects of NSAIDs

Major NSAID adverse effects are gastrointestinal (GI), cardiovascular (CV), hypersensitivity, and renal events. The NSAIDs can damage gastric, small bowel, and colonic mucosa (Ng & Chan, 2010). Risk factors for GI events are age > 65 , tobacco or alcohol use, history of peptic ulcer, longer NSAID use, use of two or more NSAIDs, and poor performance status (Pountos et al., 2011). A proton pump inhibitor (PPI; e.g., omeprazole) or histamine-2 (H₂) blocker (e.g., famotidine) decreases ulcer incidence but does not prevent severe GI complications.

Cardiovascular complications (e.g., myocardial infarction, stroke, systemic and pulmonary hypertension, congestive heart failure, and sudden cardiac death) are *more* likely with COX-2 selective (celecoxib) than nonselective NSAIDs (Grosser, 2009). Mechanisms are unclear but may relate to venous thromboembolic, blood pressure, or other effects (García Rodriguez, Tacconelli, & Patrignani, 2008). Acetaminophen or an opioid may be a safer analgesic for patients with significant CV disease (Vardeny & Solomon, 2008).

The NSAIDs cause 21% to 25% of all drug-induced respiratory, skin, or generalized hypersen-

Table 3. NSAIDs and Acetaminophen

Class/Drugs	Typical dosing	Half-Life	Comments	Adverse effects
Selective COX-2 inhibitors				
Celcoxib			No antiplatelet effect; GI complication incidence slightly lower than with nonselective NSAIDs	<ul style="list-style-type: none"> • Gastrointestinal (black box warning) <ul style="list-style-type: none"> » Mild: nausea, dyspepsia, heartburn, abdominal pain or cramps, diarrhea in 20%–40% of patients » Moderate: GI mucosal erosions and asymptomatic ulcers in 15%–30% of patients; may heal spontaneously » Severe: symptomatic ulcers, with or without bleeding—can be life-threatening (~1%–2% of users, mortality 10%)
Nonselective NSAIDs				
<i>Salicylates</i>				
Aspirin (acetylsalicylic acid)	250–500 mg q12h	0.25 h	Irreversible inhibition of platelet aggregation	<ul style="list-style-type: none"> • Cardiovascular (black box warning) <ul style="list-style-type: none"> » MI, CVA, CHF, thrombosis, sudden cardiac death » Greater risk with COX-2 inhibitor • Hypersensitivity reactions <ul style="list-style-type: none"> » Respiratory: acute—aspirin-induced or exacerbated asthma; delayed—pneumonitis » Skin: acute—urticaria, angioedema; delayed—maculopapular exanthemas, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome » Generalized: acute—anaphylaxis, severe bronchospasm within minutes » Late hypersensitivity may occur in the CNS (aseptic meningitis) or kidney (nephritis) » Lowest risk with COX-2-specific NSAID • Renal: acute kidney injury, hypertension, sodium and water retention <ul style="list-style-type: none"> » Greatest risk during initial use (first 4–6 weeks) • Renal prostaglandins affect systemic vascular resistance and may lead to hypertension, salt and water retention, edema, hyperkalemia, glomerular lesions or interstitial nephritis <ul style="list-style-type: none"> » High risk: ibuprofen, ketoprofen, fenoprofen, indomethacin, piroxicam » Intermediate risk: diclofenac, sulindac » Low risk: naproxen, nonaspirin salicylates
Salsalate	1,500 mg bid (arthritis)	1 h	Therapeutic levels: 100–300 mg/mL; toxic > 300 mg/mL	
Diflunisal	200–500 mg q12h	8–13 h		
<i>Nonacetylated salicylates</i>				
Choline magnesium trisalicylate	1,500 mg bid	2–3 h	No effect on platelets	
<i>Propionic acid derivatives</i>				
Ibuprofen	400 mg q4–6h (pain dose) 600–800 mg tid to qid (inflammation dose)	1.8–2.5 h	Reversible platelet aggregation inhibition	
Ketoprofen	25–50 mg q6–8h	2–4 h		
Naproxen	250 mg q6–8h	12–15 h	Better tolerated than indomethacin, aspirin	
Fenoprofen	300–600 mg tid to qid	2–3 h		
Flurbiprofen	50–100 mg bid to tid	5.7 h		
<i>Indoles</i>				
Indomethacin	25 mg bid to tid	4.5 h	High-anti-inflammatory, low-analgesic effect	
Sulindac	150 mg q12h	7.8–16.4 h		
<i>Fenamates</i>				
Mefenamic acid	250 mg q6h	2–3.3 h		

Note. NSAID = nonsteroidal anti-inflammatory drug; COX = cyclooxygenase; GI = gastrointestinal; bid = twice daily; CV = cardiovascular; MI = myocardial infarction; CVA = cardiovascular accident; CHF = congestive heart failure; tid = three times daily; qid = four times daily; CNS = central nervous system; IM = intramuscular; IV = intravenous; PO = oral; APAP = acetaminophen; N&V = nausea and vomiting; RUQ = right upper quadrant. Information from Amadio et al. (1993); Dart & Bailey (2007); Garzon-Rodríguez et al. (2013); Grosser (2009); Huerta et al. (2005); James & Cleland (2006); Knights et al. (2010); Kowalski et al. (2011); McGill et al. (2012); Munir et al. (2007); Musu et al. (2011); Ng & Chan (2010); Pountos et al. (2011); Sanchez-Borges (2010); Weir (2002).

☞ Table continued on next page.

Table 3. NSAIDs and Acetaminophen (cont.)

Class/Drugs	Typical Dosing	Half-Life	Comments	Adverse effects
<i>Fenamates (cont.)</i>				
Meclofenamate	100 mg tid 200-400 mg qd			<ul style="list-style-type: none"> Administer cautiously to elderly patients with already compromised renal function, heart failure, or hypertension
<i>Pyrrolo-pyrrole</i>				
Ketorolac	Initial: 30-60 mg IM or 30 mg IV; then 15-30 mg IV/IM q6h	4-7 h	May precipitate renal failure in elderly or hypovolemic patients; limit use to ≤ 5 days	
<i>Pyranocarboxyl acid</i>				
Etodolac	200-400 mg q6-8h	6-7 h		
<i>Oxicams</i>				
Piroxicam	10-20 mg qd	30-80 h	Risk for GI bleeding may be greater	
Meloxicam	7.5 mg qd (15 mg max)	16-24 h		
<i>Acetaminophen</i>	Maximum single PO dose: 1,000 mg; maximum 24-hr dose: 4,000 mg		Parenteral APAP used for postoperative pain	<ul style="list-style-type: none"> Hepatotoxicity <ul style="list-style-type: none"> » Phase 1: 0.5-24 h, asymptomatic or nonspecific symptoms (anorexia, nausea, malaise) » Phase 2: 18-72 h, N&V, RUQ pain and possible tenderness to palpation, tachycardia, hypotension secondary to volume loss » Phase 3: 72-96 h, hepatic necrosis and dysfunction, jaundice, coagulopathy, hypoglycemia, hepatic encephalopathy

Note. NSAID = nonsteroidal anti-inflammatory drug; COX = cyclooxygenase; GI = gastrointestinal; bid = twice daily; CV = cardiovascular; MI = myocardial infarction; CVA = cardiovascular accident; CHF = congestive heart failure; tid = three times daily; qid = four times daily; CNS = central nervous system; IM = intramuscular; IV = intravenous; PO = oral; APAP = acetaminophen; N&V = nausea and vomiting; RUQ = right upper quadrant. Information from Amadio et al. (1993); Dart & Bailey (2007); Garzon-Rodríguez et al. (2013); Grosser (2009); Huerta et al. (2005); James & Cleland (2006); Knights et al. (2010); Kowalski et al. (2011); McGill et al. (2012); Munir et al. (2007); Musu et al. (2011); Ng & Chan (2010); Pountos et al. (2011); Sanchez-Borges (2010); Weir (2002).

sitivity reactions (Kowalski et al., 2011). Acute hypersensitivity arises immediately to several hours after ingestion, and delayed hypersensitivity occurs > 24 hours later. Patients with hypersensitivity to one NSAID should never take moderate to strong COX inhibitors but generally tolerate weak inhibitors such as acetaminophen, celecoxib, sal-salate, and trisalicylate (Kowalski et al., 2011; Sanchez-Borges, 2010).

Renal toxicity occurs in < 1% of relatively healthy people taking a selective or nonselective NSAID but accounts for 7% of all cases of reversible or nonreversible acute renal failure (Musu et

al., 2011; Pountos et al., 2011). Renal damage is most common in the first 4 to 6 weeks, but the risk continues with long-term use. The elderly are at greatest risk because of decreased glomerular filtration rate, comorbid conditions (CV disease, hypertension, or diabetes), and taking associated drugs (e.g., β -blockers, angiotensin-converting enzyme (ACE) inhibitors, or diuretics; Huerta, Castellsague, Varas-Lorenzo, & Rodríguez, 2005; Weir, 2002).

Acetaminophen

Acetaminophen weakly inhibits COX-2 in the central nervous system, and is about as effective for

pain and fever as aspirin, but has no anti-inflammatory action (Twycross, Pace, Mihalyo, & Wilcock, 2013). Acetaminophen is well tolerated if daily doses do not exceed 4,000 mg, and single doses are ≤ 1000 mg (Munir et al., 2007). Dart and Bailey (2007) reviewed 791 research articles that included 40,202 patients taking APAP, 77% in prospective and 23% in retrospective studies. No patient in any prospective study who took APAP at 3.9 to 4 g/day for ≥ 24 hours suffered acute liver failure (ALF), underwent liver transplantation, or died. On the other hand, 32 (0.3%) of those in retrospective studies had ALF, 1 (0.01%) required liver transplantation, and 6 (0.06%) died. Conclusions were that APAP ≤ 4 g/day is not hepatotoxic, and differences in retrospective studies were probably due to mistaken recall and reporting bias or inadvertent overdoses. In November 2015, the US Food and Drug Administration (FDA)'s final guidance set the maximum APAP daily dose as 4,000 mg (rather a specific number of pills), as well as 325 mg in any combination product. The FDA warned liver damage might occur with higher doses if APAP is taken with other APAP-containing drugs or by persons with an alcohol consumption of ≥ 3 drinks/day (US Food and Drug Administration, 2016).

The minimum *single* hepatotoxic dose of APAP is 7.5 g, but repeated doses of combination APAP products (*supratherapeutic overdose*) cause about 50% of ALF cases (Larson et al., 2005; Temple & Baggish, 2005). Chronic alcoholism or liver disease increases the risk after acute overdose, but hepatotoxicity can occur in patients without liver disease. Overdoses overwhelm the minor APAP metabolic pathway, causing accumulation of *n*-acetyl-*p*-benzoquinone imine, a hepatotoxic intermediate metabolite (McGill et al., 2012). In rare instances, liver toxicity progresses to renal failure, multiorgan failure, and death. *N*-acetylcysteine administered within 8 hours after a toxic APAP dose is most effective but can be beneficial even ≥ 24 hours later (Farrell, 2016).

ADJUVANT ANALGESICS

Adjuvant (coanalgesics) have other primary indications but have been shown to decrease pain with diabetic neuropathy, postherpetic neuralgia, or HIV-related neuropathy. A few studies have focused on cancer-related neuropathic pain (Jon-

gen et al., 2013; van den Beuken-van Everdingen et al., 2016). Table 4 includes Canadian Pain Society first-line coanalgesics: tricyclic antidepressants (TCAs), serotonin norepinephrine-reuptake inhibitors (SNRIs), and gabapentinoids (Moulin et al., 2014). Lidocaine 5% patches or later-line adjuvants (e.g., older anticonvulsants, corticosteroids, and *N*-methyl-*D*-aspartate [NMDA] receptor antagonists) may help some patients (Vadalouca et al., 2012; Mitra & Jones, 2012).

Antidepressants

A meta-analysis of many small TCA studies confirmed about one-third of patients experienced almost 50% relief of neuropathic pain, and only 4% had dose-limiting adverse effects (Vadalouca et al., 2012). The TCAs may also alleviate anxiety and insomnia (Fallon, 2013). The TCAs inhibit norepinephrine and serotonin reuptake at dorsal spinal cord synapses and secondarily block neural sodium channels and NMDA glutamate receptors (Mitra & Jones, 2012). The TCAs, including secondary (desipramine and nortriptyline) and tertiary amines (amitriptyline and imipramine), have similar analgesic efficacy. However, tertiary TCAs have worse anticholinergic effects (dry mouth, constipation, and orthostasis), sedation, and cardiac effects—particularly amitriptyline, which should be used cautiously in elderly patients with congestive heart failure, ischemic heart disease, cardiac arrhythmia, or bundle branch block.

Duloxetine and venlafaxine, selective SNRIs, are effective for neuropathic pain and have fewer adverse effects than TCAs (McGeeney, 2008; Vadalouca et al., 2012). Duloxetine dosing is simple: 60 mg once or twice a day is equally effective (Dworkin et al., 2010). Duloxetine does not cause clinically important electrocardiographic or blood pressure changes. Cardiovascular effects are rare with venlafaxine, which typically decreases pain after the dose is increased from 75 mg to ≥ 150 mg/day (Fallon, 2013). Venlafaxine may also reduce hot flushes and menopausal symptoms and may be particularly useful for women with breast cancer.

Anticonvulsants

Neuropathic pain is somewhat analogous to seizures; low levels of gamma-aminobutyric acid (GABA), changes in voltage-gated calcium or so-

Table 4. Adjuvant Analgesics

	Dosing	Advantages	Adverse effects	Comments
Antidepressants				
<i>Tricyclic antidepressants (TCAs)—secondary amines</i>				
Nortriptyline Desipramine	10–25 mg at bedtime, titrate every 3–7 days as needed by 25 mg to max 200 mg	<ul style="list-style-type: none"> • Inexpensive • Convenient (once daily) • Better tolerated, as effective as amitriptyline and imipramine (tertiary amines) 	Cardiac toxicity, anticholinergic effects (e.g., orthostasis, constipation, dry mouth) more common with amitriptyline, imipramine	<ul style="list-style-type: none"> • Use cautiously for patients with ischemic heart disease, ventricular conduction abnormalities (limit \leq 100 mg/day) • Adequate trial of TCA: 6–8 weeks including 2 weeks at the highest dose
<i>Selective serotonin norepinephrine-reuptake inhibitors (SSNRIs)</i>				
Duloxetine	30 mg once daily for 1 week; then 60 mg once daily (max 120 mg daily)	<ul style="list-style-type: none"> • Simple dosing • No clinically significant cardiac, blood pressure effects 	Nausea (reduce to last dose), somnolence, dry mouth, constipation or diarrhea, sweating, dizziness	<ul style="list-style-type: none"> • Expensive agents • Duloxetine: contraindicated in patients with hepatic dysfunction • Venlafaxine: decrease dose in patients with renal or hepatic insufficiency; use cautiously in patients with heart disease, hypertension • Taper before discontinuing to prevent withdrawal syndrome
Venlafaxine	75 mg daily; titrate over 2 to 4 weeks to 150–225 mg/day	Short-, long-acting formulations	Abnormal cardiac conduction (rare), increased blood pressure	
Anticonvulsants				
<i>Calcium channel alpha-2-delta ligands</i>				
Gabapentin	Start 100 mg three times daily, increase q3–4d by 100–300 mg/day	Inexpensive	Dose-dependent dizziness, sedation, headache, diarrhea, nausea	<ul style="list-style-type: none"> • Alternate starting dose: 300 mg at bedtime to aid sleep • Gabapentin: adequate trial may take 2 months; max: 3,600 mg/day • Pregabalin: max: 600 mg/day (if creatinine clearance > 60 mL/min) • Reduce doses for renal insufficiency
Pregabalin	Divide daily dose into 2–3 doses Start 150 mg/day for 3 days; increase to 300 mg/day for 4 days; increase to 600 mg/day	Easier to escalate doses		
Topical anesthetic				
Lidocaine patches 5%	Up to 3 patches, cut to size	No systemic absorption	<ul style="list-style-type: none"> • Expensive • Minor local reactions 	Useful for localized pain

Note. Information from Dworkin et al. (2010); Fallon (2013); McGeeney (2008); Mitra & Jones (2012); Moulin et al. (2014); Vadalouca et al. (2012).

dium channels, and downregulated spinal cord GABA receptors diminish inhibitory regulation of hyperexcitable, injured nerves that fire spontaneously (Mitra & Jones, 2012; Vadalouca et al., 2012). Gabapentin and pregabalin bind to and modulate voltage-gated calcium channels, inhibit neurotransmitter release, and stabilize neuronal cell membranes (Dworkin et al., 2010; Fallon, 2013; McGeeney, 2008). Either drug usually relieves

postherpetic neuralgia, painful diabetic neuropathy, spinal cord injury pain, or neuropathic cancer pain relief within 1 to 2 weeks.

Gabapentin is inexpensive and preferred by insurers, whereas pregabalin is more expensive and usually a second-line option for patients who do not tolerate gabapentin (Mitra & Jones, 2012). Gabapentin has poor oral bioavailability and nonlinear pharmacokinetics, so doses are

escalated slowly (Dworkin et al., 2010; Vadalouca et al., 2012). The usual starting dose is 100 mg three times per day, but a single 300-mg dose at bedtime may aid sleep and minimize daytime sleepiness. Pregabalin has linear pharmacokinetics, so dosing is straightforward. Patients who tolerate the first dose level (150 mg/day) but do not attain pain relief can be increased to 300 mg/day after 1 week and to 600 mg/day a week later.

Topical Lidocaine

Topical lidocaine 5% patches may be used alone or with other drugs and reduce ectopic voltage-gated sodium channel activity in damaged sensory nerves without affecting normal sensation (Fallon, 2013; Garzón-Rodríguez, Merchan, Calsina-Berna, Lopez-Romboli, & Porta-Sales, 2013; McGeeney, 2008). They are helpful for about 25% of patients with postherpetic neuralgia or other localized neuropathic pain, such as painful mastectomy or thoracotomy scar, or rib cage or subcutaneous tumor.

Up to three lidocaine patches are cut to shape and applied to *intact* skin for 12 hours, during which 5% of the patch dose is absorbed, and then removed for 12 hours (McGeeney, 2008). In practice, patches are often left on for longer times because patients fear return of pain if patches are removed, and adherence to the 12-hour on-and-off schedule may be difficult. Pharmacokinetic studies have confirmed four patches are safe and well tolerated for 3 consecutive days, whether reapplied every 12 or 24 hours (Gammaitoni, Alvarez, & Galer, 2002). No differences in plasma lidocaine concentrations with either application schedule were noted, and serum lidocaine levels reached only 14% of the antiarrhythmic dose. This lack of systemic effects means dose adjustments for renal or hepatic dysfunction are not necessary (Fallon, 2013; McGeeney, 2008).

Other Adjuvant Agents

There are no randomized or adequately powered studies of second- or later-line adjuvant drugs (other anticonvulsants, corticosteroids, antispasmodics, cannabinoids, or ketamine), which might be tried if first-line adjuvant drugs are ineffective or intolerable, or for other indications (Dworkin et

al, 2010). For instance, clonazepam, a long-acting benzodiazepine with anticonvulsant effects, is often helpful for myoclonic jerks as well as anxiety (Caviness, 2014; Van Zanducke, 2003). Slow escalation minimizes the risk for ataxia and sleepiness. Oxcarbazepine, carbamazepine, and topiramate are anticonvulsants that suppress sodium channel-mediated ectopic neuronal discharges, and baclofen, an antispasmodic, GABA-B agonist, is sometimes tried for neuropathic pain (McGeeney, 2008; Mitra & Jones, 2012; Vadalouca et al., 2012).

Corticosteroids are typically used for painful inflammation with serious conditions, such as tumor-related bony epidural compression or nerve root inflammation (Leppert & Buss, 2012; Mitra & Jones, 2012; Prommer, 2015; Vadalouca et al., 2012). Inflammation or compression can also be problematic with radiation therapy (RT)-induced “flare,” particularly with whole-brain or spinal RT, from primary brain tumors or metastasis-induced cerebral edema, or hepatomegaly-related liver capsule pain.

Dexamethasone is most often used because of low mineralocorticoid and fluid retention effects as well as a long half-life (36–54 hours) allowing once-per-day dosing. Dexamethasone administration in the late afternoon or evening prevents corticosteroid stimulant effects and sleep disturbances (McGeeney, 2008). A small oral dose (dexamethasone 1 or 2 mg twice a day) may benefit patients with nonemergent problems such as pain poorly responsive to opioids and dose titration as needed. Conversely, patients with impending spinal cord compression or another emergent problem may be started on a higher dose (16 mg to 96 mg/day) and rapidly titrated down to a minimally effective dose (Prommer, 2015). Dose-related adverse effects may include hyperglycemia, hypertension, fluid retention, immunosuppression, GI, and neuropsychologic effects.

Hyoscine (scopolamine) or octreotide may alleviate colicky abdominal pain or spasms from partial or total bowel obstruction. Hyoscine has antispasmodic and local anticholinergic effects in the gut at smooth muscle muscarinic receptors; induces smooth muscle relaxation; and reduces pathologically enhanced peristalsis, gut motility, and cramping (Soares & Chan, 2007; Tytgat, 2007). Hyoscine does not cross the blood-brain

barrier and has a low incidence of systemic anticholinergic adverse events. Continuous intravenous infusion, 60 mg over 24 hours, may control pain from inoperable bowel obstruction (Soares & Chan, 2007). Octreotide, a somatostatin analogue, reduces gastric, pancreatic and intestinal secretions, and GI motility. It is similarly effective as hyoscine for colicky pain and may have a more rapid onset.

Cannabis, which has been used medicinally for thousands of years, comprises numerous phytocannabinoids that may be synergistic with opioids and have antiemetic and appetite stimulating effects (Abrams, 2016; Fallon, 2013; Moulin et al., 2014). Exogenous and endocannabinoids bind to cannabinoid receptors (CB1 and CB2) throughout the central nervous system and periphery to influence intracellular signaling (Russo & Hohmann, 2015; Whiting et al., 2015).

Physiologic effects of cannabinoids include pain modulation at peripheral, spinal, and supraspinal levels, which decreases neuropathic pain, hyperalgesia, and inflammation. Cannabinoids are usually well tolerated, with gradual dose increases, but adverse effects may include dizziness, drowsiness, impaired psychomotor function, dry mouth, and dysphoria. Sativex, an oromucosal cannabinoid spray for cancer-related pain, is available in Canada and Europe. In the United States, cannabis is currently classified as a Schedule I substance (no accepted medical use and high abuse potential), which impedes research. The sociopolitical climate seems to be changing, and the number of states permitting medical (and recreational) marijuana use is increasing. Clinicians must know about cannabis status in their state and review research and clinical evidence for use, as well as differences in commercial products and marijuana (Savage et al., 2016).

Ketamine, structurally similar to phencyclidine, is a dissociative anesthetic and noncompetitive NMDA antagonist in descending spinal inhibitory pathways (Niesters, Martini, & Dahan, 2013). Ketamine can induce dose-related psychotropic adverse effects (e.g., auditory or visual hallucinations, paranoid ideation, panic attacks, nightmares or vivid dreams, and an unpleasant or euphoric drug high). Cardiovascular effects (e.g., tachycar-

dia and hypertension) can occur after low-dose ketamine infusion (Niesters et al., 2013). A sub-anesthetic dose trial may be done for difficult to control or intractable neuropathic, inflammatory, or ischemic pain resistant to other options (McGeeney, 2008). Loveday & Sindt (2015) reported that patients with intractable pain treated with subanesthetic, weight-based CIV ketamine (per university hospital protocol) usually had mild and transient side effects controlled with low-dose benzodiazepine or haloperidol.

CONCLUSION

Oncology APs, wherever they practice, have important roles and opportunities to optimize pain management in cancer patients. Collaborative, interprofessional roles with other APs, oncology pharmacists, oncologists, and others may identify personal or professional colleague knowledge gaps and potential learning opportunities, such as interprofessional pain management rounds. ●

Disclosure

Dr. Wickham has received consulting fees/honorarium from Insys Therapeutics, Inc.

References

- Abrams, D. I. (2016). Integrating cannabis into clinical cancer care. *Current Oncology*, 23(Suppl 2), S8–S14. <https://doi.org/10.3747/co.23.3099>
- Amadio, P., Cummings, D. M., & Amadio, P. (1993). Nonsteroidal anti-inflammatory drugs: Tailoring therapy to achieve results and avoid toxicity. *Postgraduate Medicine*, 93(4), 73–97. <https://doi.org/10.1080/00325481.1993.11701639>
- American Psychiatric Association (APA). (2013). Substance-related and addictive disorders. Retrieved from https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM-5-Substance-Use-Disorder.pdf
- American Society of Addiction Medicine. (2011). Quality & practice: Definition of addiction. Retrieved from <http://www.asam.org/quality-practice/definition-of-addiction>
- American Society of Clinical Oncology (ASCO). (2016). ASCO releases principles for balancing appropriate patient access to prescription opioids with curbing misuse, abuse of these drugs. Retrieved from <https://www.asco.org/advocacy-policy/asco-in-action/asco-releases-principles-balancing-appropriate-patient-access>
- Barclay, J. S., Owens, J. E., & Blackhall, L. J. (2014). Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen. *Supportive Care in Cancer*, 22(7), 1883–1888. <https://doi.org/10.1007/s00520-014-2167-6>
- Bedard, G., Hawley, P., Zhang, L., Slaven, M., Gagnon, P., Bisland, S.,...Chow, E. (2013). A survey of Canadian cancer patients' perspectives on the characteristics and treat-

- ment of breakthrough pain. *Supportive Care in Cancer*, 21(9), 2557–2563. <https://doi.org/10.1007/s00520-013-1817-4>
- Breuer, B., Fleishman, S. B., Cruciani, R. A., & Portenoy, R. K. (2011). Medical oncologists' attitudes and practice in cancer pain management: A national survey. *Journal of Clinical Oncology*, 29(36), 4769–4775. <https://doi.org/10.1200/JCO.2011.35.0561>
- Brunelli, C., Zecca, E., Martini, C., Campa, T., Fagnoni, E., Bagnasco, M.,...Caraceni, A. (2010). Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. *Health and Quality of Life Outcomes*, 8, 42. <https://doi.org/10.1186/1477-7525-8-42>
- Caraceni, A., Martini, C., Zecca, E., & Portenoy, R. K. (2004). Breakthrough pain characteristics and syndromes in patients with cancer pain: An international survey. *Palliative Medicine*, 18(3), 177–183. <https://doi.org/10.1191/0269216304pm8900a>
- Caraceni, A., & Portenoy, R. K. (1999). An international survey of cancer pain characteristics and syndromes. *Pain*, 82(3), 263–274. [https://doi.org/10.1016/S0304-3959\(99\)00073-1](https://doi.org/10.1016/S0304-3959(99)00073-1)
- Caviness, J. N. (2014). Treatment of myoclonus. *Neurotherapeutics*, 11(1), 188–200. <https://doi.org/10.1007/s13311-013-0216-3>
- Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). Retrieved from <http://www.samhsa.gov/data/>
- Chang, V. T., Janian, N., Jain, S., & Chau, C. (2006). Regional cancer pain syndromes. *Journal of Palliative Medicine*, 9(6), 1435–1453. <https://doi.org/10.1089/jpm.2006.9.1435>
- Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry*, 71(7), 821–826. <https://doi.org/10.1001/jamapsychiatry.2014.366>
- Dalal, S., Hui, D., Nguyen, L., Chacko, R., Scott, C., Roberts, L., & Bruera, E. (2012). Achievement of personalized pain goal in cancer patients referred to a supportive care clinic at a comprehensive cancer center. *Cancer*, 118, 3869–3677. <https://doi.org/10.1002/cncr.26694>
- Daeninck, P., Gagnon, B., Gallagher, R., Henderson, J. D., Shir, Y., Zimmermann, C., & Lapointe, B. (2016). Canadian recommendations for the management of breakthrough cancer pain. *Current Oncology*, 23(2), 96–108. <https://doi.org/10.3747/co.23.2865>
- Dart, R. C., & Bailey, E. (2007). Does therapeutic use of acetaminophen cause acute liver failure? *Pharmacotherapy*, 27(9), 1219–1230. <https://doi.org/10.1592/phco.27.9.1219>
- Davies, A., Buchanan, A., Zeppetella, G., Porta-Sales, J., Likar, R., Weismayr, W.,...Stenberg, M. (2013). Breakthrough cancer pain: An observational study of 1000 European oncology patients. *Journal of Pain and Symptom Management*, 46(5), 619–628. <https://doi.org/10.1016/j.jpainsymman.2012.12.009>
- Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain. *Recommendations and Reports*, 65(1), 1–49. Retrieved from <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>
- Duke, G., Haas, B. K., Yarbrough, S., & Northam, S. (2013). Pain management knowledge and attitudes of baccalaureate nursing students and faculty. *Pain Management Nursing*, 14(1), 11–19. <https://doi.org/10.1016/j.pmn.2010.03.006>
- Dworkin, R. H., Jensen, M. P., Gammaitoni, A. R., Olaleye, D. O., & Galer, B. S. (2007). Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *Journal of Pain*, 8(2), 118–126. <https://doi.org/10.1016/j.jpain.2006.06.005>
- Dworkin, R. H., O'Connor, A. B., Audette, J., Baron, R., Gourlay, G. K., Haanpaa, M. L.,...Wells, C. D. (2010). Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings*, 85(3 suppl), S3–S14. <https://doi.org/10.4065/mcp.2009.0649>
- Eisenberg, E., Marinangeli, F., Birkhahn, J., Paladini, A., & Varrassi, G. (2005). Time to modify the WHO analgesic ladder? *Pain: Clinical Updates*, 13(5), 1–4. Retrieved from <https://www.iasp-pain.org/PublicationsNews/NewsletterIssue.aspx?ItemNumber=2121>
- Epstein, J. B., Wilkie, D. J., Fischer, D. J., Kim, Y. O., & Villines, D. (2009). Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. *Head & Neck Oncology*, 1(26). <https://doi.org/10.1186/1758-3284-1-26>
- Fallon, M. T. (2013). Neuropathic pain in cancer. *British Journal of Anaesthesia*, 111(1), 105–111. <https://doi.org/10.1093/bja/aet208>
- Farrell, S. E. (2016). Acetaminophen toxicity. Retrieved from emedicine.medscape.com/article/820200-overview
- Ferreira-Valente, M., Pais-Ribeiro, J. L., & Jensen, M. P. (2011). Validity of four pain intensity rating scales. *Pain*, 152(10), 2399–2404. <https://doi.org/10.1016/j.pain.2011.07.005>
- Fisch, M. J., Lee, J.-W., Weiss, M., Wagner, L. I., Chang, V. T., Cella, D.,...Cleeland, C. S. (2012). Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *Journal of Clinical Oncology*, 30(16), 1980–1988. <https://doi.org/10.1200/JCO.2011.39.2381>
- Gammaitoni, A. R., Alvarez, N. A., & Galer, B. S. (2002). Pharmacokinetics and safety of continuously applied lidocaine patches 5%. *American Journal of Health System Pharmacy*, 59(22), 2215–2220. Retrieved from <http://www.ajhp.org/content/59/22/2215.long?ssoc-checked=true>
- García Rodríguez, L. A., Tacconelli, S., & Patrignani, P. (2008). Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *Journal of the American College of Cardiology*, 52(20), 1628–1636. <https://doi.org/10.1016/j.jacc.2008.08.041>
- Garzón-Rodríguez, C., Merchan, M. C., Calsina-Berna, A., López-Rómboli, E., & Porta-Sales, J. (2013). Lidocaine 5% patches as an effective short-term co-analgesic in cancer pain: Preliminary results. *Supportive Care in Cancer*, 21(11), 3153–3158. <https://doi.org/10.1007/s00520-013-1948-7>
- Gilron, I., & Jensen, M. P. (2011). Clinical trial methodology of pain treatment studies: Selection and measurement of self-report primary outcomes for efficacy. *Regional Anesthesia and Pain Medicine*, 36(4), 374–381. <https://doi.org/10.1097/AAP.0b013e318217a635>
- Gilron, I., Tu, D., & Holden, R. R. (2013). Sensory and affective pain descriptors respond differentially to pharmacological interventions in neuropathic conditions. *Clinical*

- Journal of Pain*, 29(2), 124–131. <https://doi.org/10.1097/AJP.0b013e31824ce65c>
- Glare, P. A., Davies, P. S., Finlay, E., Gulati, A., Lemanne, D., Moryl, N.,...Syrjala, K. L. (2014). Pain in cancer survivors. *Journal of Clinical Oncology*, 32(16), 1739–1747. <https://doi.org/10.1200/JCO.2013.52.4629>
- Greco, M. T., Corli, O., Montanari, M., Deandrea, S., Zagonel, V., & Apolone, G. (2011). Epidemiology and pattern of care of breakthrough cancer pain in a longitudinal sample of cancer patients. *Clinical Journal of Pain*, 27(1), 9–18. <https://doi.org/10.1097/AJP.0b013e3181edc250>
- Grosser, T. (2009). Variability in the response to cyclooxygenase inhibitors: Toward the individualization of nonsteroidal anti-inflammatory drug therapy. *Journal of Investigative Medicine*, 57(6), 709–716. <https://doi.org/10.2310/JIM.0b013e3181b04d1f>
- Gunnarsdottir, S., Donovan, H. S., Serlin, R. C., Voge, C., & Ward, S. (2002). Patient-related barriers to pain management: The Barriers Questionnaire II (BQ-II). *Pain*, 99(3), 385–396. [https://doi.org/10.1016/S0304-3959\(02\)00243-9](https://doi.org/10.1016/S0304-3959(02)00243-9)
- Halabi, S., Vogelzang, N. J., Kornblith, A. B., Ou, S.-S., Kantoff, P. W., Dawson, N. A., & Small, E. J. (2008). Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. *Journal of Clinical Oncology*, 26(15), 2544–2549. <https://doi.org/10.1200/JCO.2007.15.0367>
- Hartney, E. (2016). DSM 5 criteria for substance use disorders. Retrieved from <https://www.verywell.com/dsm-5-criteria-for-substance-use-disorders-21926>
- Hartrick, C. T., Kovan, J. P., & Shapiro, S. (2003). The numeric rating scale for clinical pain measurement: A ratio measure? *Pain Practice*, 3(4), 310–316. <https://doi.org/10.1111/j.1530-7085.2003.03034.x>
- Heit, H. A. (2003). Addiction, physical dependence, and tolerance: Precise definitions to help clinicians evaluate and treat chronic pain patients. *Journal of Pain & Palliative Care Pharmacotherapy*, 17(1), 15–29. https://doi.org/10.1080/J354v17n01_03
- Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H.,...Kaasa, S. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management*, 41(6), 1073–1093. <https://doi.org/10.1016/j.jpainsymman.2010.08.016>
- Holtan, A., & Kongsgaard, U. E. (2009). The use of pain descriptors in cancer patients. *Journal of Pain and Symptom Management*, 38(2), 208–215. <https://doi.org/10.1016/j.jpainsymman.2008.08.008>
- Huerta, C., Castellsague, J., Varas-Lorenzo, C., & Rodríguez, L. A. G. (2005). Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Disease*, 45(3), 531–539. <https://doi.org/10.1053/j.ajkd.2004.12.005>
- Hui, D., & Bruera, E. (2014). A personalized approach to assessing and managing pain in patients with cancer. *Journal of Clinical Oncology*, 32(16), 1640–1646. <https://doi.org/10.1200/JCO.2013.52.2508>
- Hunter, J., Watt-Watson, J., McGillion, M., Raman-Wilms, L., Cockburn, L., Leila, L.,...Salter, M. (2008). An interfaculty pain curriculum: Lessons learned from six years' experience. *Pain*, 140(1), 74–86. <https://doi.org/10.1016/j.pain.2008.07.010>
- Institute of Medicine. (2011). *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press. Retrieved from <http://www.nap.edu/catalog/13172/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care>
- James, M. J., & Cleland, L. G. (2006). Cyclooxygenase-2 inhibitors: What went wrong? *Current Opinion in Clinical Nutrition and Metabolic Care*, 9(2), 89–89. <https://doi.org/10.1097/01.mco.0000214565.67439.83>
- Jongen, J. L. M., Huijsman, M. L., Jessurun, J., Ogenio, K., Schipper, D., Verkouteren, D. R. C.,...Vissers, K. C. (2013). The evidence for pharmacologic treatment of neuropathic cancer pain: Beneficial and adverse effects. *Journal of Pain and Symptom Management*, 46(4), 581–590. <https://doi.org/10.1016/j.jpainsymman.2012.10.230>
- Kerba, M., Wu, J. Y., Duan, Q., Hagen, N. A., & Bennett, M. I. (2010). Neuropathic pain features in patients with bone metastases referred for palliative radiotherapy. *Journal of Clinical Oncology*, 28(33), 4892–4897. <https://doi.org/10.1200/JCO.2010.28.6559>
- Kirkby, N. S., Zaiss, A. K., Wright, W. R., Jiao, J., Chan, M. V., Warner, T. D.,...Mitchell, J. A. (2013). Differential COX-2 induction by viral and bacterial PAMPs: Consequences for cytokine and interferon responses and implications for anti-viral COX-2 directed therapies. *Biochemical and Biophysical Research Communications*, 438(2), 249–256. <https://doi.org/10.1016/j.bbrc.2013.07.006>
- Knights, K. M., Mangoni, A. A., & Miners, J. O. (2010). Defining the COX inhibitor selectivity of NSAIDs: Implications for understanding toxicity. *Expert Review of Clinical Pharmacology*, 3(6), 769–776. <https://doi.org/10.1586/ecp.10.120>
- Kowalski, M. L., Makowska, J. S., Blanca, M., Bavbek, S., Bochenek, G., Bousquet, J.,...Brockow, K. (2011). Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs): Classification, diagnosis and management: Review of the EAACI/ENDA(®) and GA2LEN/HANNA*. *Allergy*, 66(7), 818–829. <https://doi.org/10.1111/j.1398-9995.2011.02557.x>
- Kwon, J. H. (2014). Overcoming barriers in cancer pain management. *Journal of Clinical Oncology*, 32(16), 1727–1733. <https://doi.org/10.1200/JCO.2013.52.4827>
- Larson, A. M., Polson, J., Fontana, R. J., Davern, T. J., Lalani, E., Hynan, L. S.,...Lee, W. M. (2005). Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology*, 42(6), 1364–1372. <https://doi.org/10.1002/hep.20948>
- Leppert, W., & Buss, T. (2012). The role of corticosteroids in the treatment of pain in cancer patients. *Current Pain and Headache Reports*, 16(4), 307–313. <https://doi.org/10.1007/s11916-012-0273-z>
- Loveday, B. A., & Sindt, J. (2015). Ketamine protocol for palliative care in cancer patients with refractory pain. *Journal of the Advanced Practice in Oncology*, 6(6), 555–561. <https://doi.org/10.6004/jadpro.6.6.4>
- Mackey, S., Carroll, I., Emir, B., Murphy, T. K., Whalen, E., & Dumenciz, L. (2012). Sensory pain qualities in neuropathic pain. *Journal of Pain*, 13(1), 58–63. <https://doi.org/10.1016/j.jpain.2011.10.002>
- Maltoni, M., Scarpi, E., Modonesi, C., Passardi, A., Calpona, S., Turriziani, A.,...Amadori, D. (2005). A validation study of the WHO analgesic ladder: A two-step vs three-step

- strategy. *Supportive Care in Cancer*, 13, 888–894. <https://doi.org/10.1007/s00520-005-0807-6>
- Matthie, N., & McMillan, S. C. (2014). Pain: A descriptive study in patients with cancer. *Clinical Journal of Oncology Nursing*, 18(2), 205–210. <https://doi.org/10.1188/14.CJON.205-210>
- McGeeney, B. E. (2008). Adjuvant agents in cancer pain. *Clinical Journal of Pain*, 24, S14–S20. <https://doi.org/10.1097/AJP.0b013e31816b5976>
- McGill, M. R., Sharpe, M. R., Williams, C. D., Taha, M., Curry, S. C., & Jaeschke, H. (2012). The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation. *Journal of Clinical Investigation*, 122(4), 1574–1583. <https://doi.org/10.1172/JCI159755>
- McMillan, S. C., Tofthagen, C., & Morgan, M. A. (2008). Relationships among pain, sleep disturbances, and depressive symptoms in outpatients from a comprehensive cancer center. *Oncology Nursing Forum*, 35(4), 603–611. <https://doi.org/10.1188/08.ONF.603-611>
- Minami, S., Fujimoto, K., Ogata, Y., Yamamoto, S., & Komuta, K. (2015). Opioids have no negative effect on the survival time of patients with advanced lung cancer in an acute care hospital. *Supportive Care in Cancer*, 23(8), 2245–2254. <https://doi.org/10.1007/s00520-014-2592-6>
- Mitra, R., & Jones, S. (2012). Adjuvant analgesics in cancer pain: A review. *American Journal of Hospice & Palliative Medicine*, 29(1), 70–79. <https://doi.org/10.1177/1049909111413256>
- Moulin, D. E., Boulanger, A., Clark, A. J., Clarke, H., Dao, T., Finley, G. A.,...Williamson, O. D. (2014). Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. *Pain Research and Management*, 19(6), 328–335. <https://doi.org/10.1155/2014/754693>
- Munir, M. A., Enany, N., & Zhang, J.-M. (2007). Nonopioid analgesics. *Medical Clinics of North America*, 91(1), 97–111. <https://doi.org/10.1016/j.mcna.2006.10.011>
- Murinson, B. B., Gordin, V., Flynn, S., Driver, L. C., Gallagher, R. M., & Grabojs, M. (2013). Recommendations for a new curriculum in pain medicine for medical students: Toward a career distinguished by competence and compassion. *Pain Medicine*, 14(30), 345–350. <https://doi.org/10.1111/pme.12051>
- Musu, M., Finco, G., Antonucci, R., Polatie, E., Sanna, D., Evangelista, M.,...Fanos, V. (2011). Acute nephrotoxicity of NSAID from the foetus to the adult. *European Review for Medical and Pharmacological Sciences*, 15(12), 1461–1472.
- National Institute on Drug Abuse. (2016). Media guide: The science of drug abuse and addiction: The basics. Retrieved from <https://www.drugabuse.gov/publications/media-guide/dear-journalist>
- Ng, S. C., & Chan, F. K. (2010). NSAID-induced gastrointestinal and cardiovascular injury. *Current Opinion in Gastroenterology*, 26(6), 611–617. <https://doi.org/10.1097/MOG.0b013e32833e91eb>
- Niesters, M., Martini, C., & Dahan, A. (2013). Ketamine for chronic pain: Risks and benefits. *British Journal of Clinical Pharmacology*, 77(2), 357–367. <https://doi.org/10.1111/bcp.12094>
- Norko, M. A., & Fitch, W. L. (2014). DSM-5 and substance use disorders: Clinicolegal implications. *Journal of the American Academy of Psychiatry and the Law*, 42(4), 443–452. Retrieved from <http://jaapl.org/content/42/4/443/tab-article-info>
- Paice, J. A. (2010). Pain at the end of life. In B. F. Ferrell & N. Coyle (Eds.), *Oxford textbook of palliative nursing (3rd ed.)* (pp. 161–185). New York, NY: Oxford University Press.
- Paice, J. A., & Ferrell, B. (2011). The management of cancer pain. *CA: A Cancer Journal for Clinicians*, 61(3), 157–182. <https://doi.org/10.3322/caac.20112>
- Paice, J. A., & Von Roenn, J. H. (2014). Under- or overtreatment of pain in the patient with cancer: How to achieve proper balance. *Journal of Clinical Oncology*, 32(16), 1721–1726. <https://doi.org/10.1200/JCO.2013.52.5196>
- Pasternak, G. W. (2014). Opiate pharmacology and relief of pain. *Journal of Clinical Oncology*, 32(16), 1655–1661. <https://doi.org/10.1200/JCO.2013.53.1079>
- Portenoy, R. K., & Ahmed, E. (2014). Principles of opioid use in cancer pain. *Journal of Clinical Oncology*, 32(16), 1662–1670. <https://doi.org/10.1200/JCO.2013.52.5188>
- Portenoy, R. K., Sibirceva, U., Smout, R., Horn, S., Connor, S., Blum, R. H.,...Fine, P. G. (2006). Opioid use and survival at the end of life: A survey of a hospice population. *Journal of Pain and Symptom Management*, 32(6), 532–540. <https://doi.org/10.1016/j.jpainsymman.2006.08.003>
- Pountos, I., Georgouli, T., Bird, H., & Giannoudis, P. V. (2011). Nonsteroidal anti-inflammatory drugs: Prostaglandins, indications, and side effects. *International Journal of Interferon, Cytokine and Mediator Research*, 3, 19–27. <https://doi.org/10.2147/IJICMR.S10200>
- Prommer, E. E. (2015). Pharmacological management of cancer-related pain. *Cancer Control - Journal of the Moffitt Cancer Center*, 22(4), 412–425.
- Reid, C. M., Goberman-Hill, R., & Hank, G. W. (2008). Opioid analgesics for cancer pain: Symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. *Annals of Oncology*, 19(1), 44–48. <https://doi.org/10.1093/annonc/mdm462>
- Ripamonti, C. I., Santini, D., Maranzano, E., Berti, M., & Roila, F. (2012). Management of cancer pain: ESMO clinical practice guidelines. *Annals of Oncology*, 23(Suppl 7), viii139–viii154. <https://doi.org/10.1093/annonc/mds233>
- Russo, E. B., & Hohmann, A. G. (2015). Role of cannabinoids in pain management. In T. R. Deer, M. S. Leong, A. Buvanendran, V. Gordin, P. S. Kim, S. J. Panchal, & A. L. Ray (Eds.), *Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches* (pp. 181–197). New York, NY: Springer-Verlag.
- Sanchez-Borges, M. (2010). NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Medical Clinics of North America*, 94(4), 853–864. <https://doi.org/10.1016/j.mcna.2010.03.005>
- Savage, S. R., Romero-Sandoval, A., Schatman, M., Wallace, M., Fanciullo, G., McCarberg, B., & Ware, M. (2016). Cannabis in pain treatment: Clinical and research considerations. *Journal of Pain*, 17(6), 654–668. <https://doi.org/10.1016/j.jpain.2016.02.007>
- Shaiyov, L. (2006). Difficult pain syndromes: Bone pain, visceral pain, and neuropathic pain. *Cancer Journal*, 12(5), 330–340. <https://doi.org/10.1097/00130404-200609000-00002>
- Situ, D., Wang, J., Shao, W., & Zhu, Z.-H. (2012). Assessment and treatment of cancer pain: From Western to Eastern.

- Annals of Palliative Medicine*, 1(1), 32–44. <https://doi.org/10.3978/j.issn.2224-5820.2011.10.01>
- Soares, L. G., & Chan, V. W. (2007). The rationale for a multimodal approach in the management of breakthrough cancer pain: A review. *American Journal of Hospice & Palliative Medicine*, 24(5), 430–439. <https://doi.org/10.1177/1049909107302297>
- Stein, K. D., Alcaraz, K. I., Kamson, C., Fallon, E. A., & Smith, T. G. (2015). Sociodemographic inequalities in barriers to cancer pain management: A report from the American Cancer Society's Study of Cancer Survivors-II (SCS-II). *Psycho-Oncology*, 25(10), 1212–1221. <https://doi.org/10.1002/pon.4218>
- Stute, P., Lehmann, K. A., & Grond, S. (2001). Symptoms during cancer pain treatment following WHO-guidelines: A longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*, 93(3), 247–257. [https://doi.org/10.1016/S0304-3959\(01\)00324-4](https://doi.org/10.1016/S0304-3959(01)00324-4)
- Swarm, R., Abernethy, A. P., Angheliescu, D. L., Benedetti, C., Blinderman, C. D., Boston, B.,...Weinstein, S. W. (2010). Adult cancer pain. *Journal of the National Comprehensive Cancer Network*, 8(9), 1046–1086. <https://doi.org/10.6004/jnccn.2010.0076>
- Tavoli, A., Montazeri, A., Roshan, R., Tavoli, Z., & Melyani, M. (2008). Depression and quality of life in cancer patients with and without pain: The role of pain beliefs. *BMC Cancer*, 8, 177. <https://doi.org/10.1186/1471-2407-8-177>
- te Boveltd, N., Vernooij-Dassen, M., Burger, N., IJsseldijk, M., Vissers, K., & Engels, Y. (2013). Pain and its interference with daily activities in medical oncology outpatients. *Pain Physician*, 16(4), 379–389. Retrieved from <http://www.painphysicianjournal.com/linkout?issn=1533-3159&vol=16&page=379>
- Temple, A. R., & Baggish, J. S. (2005). Guidelines for the management of acetaminophen overdose (McNeil Consumer & Specialty Pharmaceuticals monograph). Retrieved from <http://www.supplements.annemergmed.com/sites/default/files/A-Overdoes%20Guidelines.pdf>
- Twycross, R., Pace, V., Mihalyo, M., & Wilcock, A. (2013). Therapeutic reviews: Acetaminophen (paracetamol). *Journal of Pain and Symptom Management*, 46(5), 747–755. <https://doi.org/10.1016/j.jpainsymman.2013.08.001>
- Tytgat, G. N. (2007). Hyoscine butylbromide: A review of its use in the treatment of abdominal cramping and pain. *Drugs*, 67(9), 1343–1357. <https://doi.org/10.2165/00003495-200767090-00007>
- US Food and Drug Administration. (2016). Notice to industry: Final guidance for over-the-counter products that contain acetaminophen. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm310469.htm>
- Vadalouca, A., Raptis, E., Moka, E., Zis, P., Sykioti, P., & Siafaka, I. (2012). Pharmacological treatment of neuropathic cancer pain: A comprehensive review of the current literature. *Pain Practice*, 12(3), 219–251. <https://doi.org/10.1111/j.1533-2500.2011.00485.x>
- Vallerand, A. H., Collins-Bohler, D., Templin, T., & Hasenau, S. M. (2007). Knowledge of and barriers to pain management in caregivers of cancer patients receiving homecare. *Cancer Nursing*, 30(1), 31–37. <https://doi.org/10.1097/00002820-200701000-00006>
- van den Beuken-van Everdingen, M. H. J., de Graeff, A., Jongen, J. L. M., Dijkstra, D., Mostovaya, I., & Vissers, K. C. (2016). Pharmacological treatment of pain in cancer patients: The role of adjuvant analgesics, a systematic review. *Pain Practice*, 17(3), 409–419. <https://doi.org/10.1111/papr.12459>
- Van Zanducke, M. (2003). Treatment of myoclonus. *Acta Neurologica Belgica*, 103, 66–70.
- Vardeny, O., & Solomon, S. D. (2008). Cyclooxygenase-2 inhibitors, nonsteroidal anti-inflammatory drugs, and cardiovascular risk. *Cardiology Clinics*, 26(4), 589–601. <https://doi.org/10.1016/j.ccl.2008.06.004>
- Vargas-Schaffer, G. (2010). Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Canadian Family Physician*, 56(6), 514–517. Retrieved from <http://www.cfp.ca/content/56/6/514/tab-article-info>
- Viale, P. H. (2016). The passage of CARA: Implications for patients with cancer pain. *Journal of the Advanced Practitioner in Oncology*, 7(6), 590–592. <https://doi.org/10.6004/jadpro.2016.7.6.1>
- Volkow, N. D., & McLellan, A. T. (2016). Opioid abuse in chronic pain—Misconceptions and mitigation strategies. *New England Journal of Medicine*, 374, 1253–1263. <https://doi.org/10.1056/NEJMr1507771>
- von Gunten, C. F. (2016). The pendulum swings for opioid prescribing. *Journal of Palliative Medicine*, 19(4), 348. <https://doi.org/10.1089/jpm.2016.0079>
- Webber, K., Davies, A. N., & Cowie, M. R. (2016). Disparities between clinician and patient perception of breakthrough pain control. *Journal of Pain and Symptom Management*, 51(5), 933–937. <https://doi.org/10.1016/j.jpainsymman.2015.12.309>
- Weir, M. R. (2002). Renal effects of nonselective NSAIDs and coxibs. *Cleveland Clinic Journal of Medicine*, 69(suppl 1), S1–53–S1–58. <https://doi.org/10.3949/ccjm.69.Suppl.1.S153>
- Weissman, D. E., & Haddox, J. D. (1989). Opioid pseudoaddiction—An iatrogenic syndrome. *Pain*, 36(3), 363–366. [https://doi.org/10.1016/0304-3959\(89\)90097-3](https://doi.org/10.1016/0304-3959(89)90097-3)
- Wells, N., McDowell, M. R., Hendricks, P., Dietrich, M. S., & Murphy, B. (2011). Cancer pain management in ambulatory care: Can we link assessment and action to outcomes? *Supportive Care in Cancer*, 19(11), 1865–1871. <https://doi.org/10.1007/s00520-010-1030-7>
- Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V.,...Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA*, 313(24), 2456–2473. <https://doi.org/10.1001/jama.2015.6358>
- World Health Organization (WHO). (1987). *Cancer Pain Relief*. Geneva, Switzerland: WHO.
- Zech, D. F. J., Grond, S., Lynch, J., Herte, D. L., & Lehmann, K. A. (1995). Validation of World Health Organization guidelines for cancer pain relief: A 10-year prospective study. *Pain*, 63(1), 65–76. [https://doi.org/10.1016/0304-3959\(95\)00017-M](https://doi.org/10.1016/0304-3959(95)00017-M)