Cancer pain management: Use of acetaminophen and nonsteroidal anti-inflammatory drugs

AUTHORS: Russell K Portenoy, MD, Ebtesam Ahmed, PharmD, MS, Yair Y Keilson, MD
SECTION EDITOR: Janet Abrahm, MD
DEPUTY EDITOR: Melinda Yushak, MD, MPH

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INTRODUCTION

Opioid therapy is the first-line approach for moderate or severe chronic pain in populations with active cancer (see "Cancer pain management with opioids: Optimizing analgesia"). However, the comprehensive management of pain in patients with cancer also requires expertise in the use of the nonopioid analgesics, such as acetaminophen (also known as paracetamol), non-steroidal anti-inflammatory agents (NSAIDs), and a group of drugs referred to as "adjuvant" analgesics or coanalgesics.

A stepwise approach to management of cancer pain that includes both opioid and nonopioid drugs is endorsed by several bodies, including the World Health Organization (WHO). Mild pain can initially be managed with non-opioid drugs (eg, acetaminophen or an NSAID) with or without an analgesic adjuvant, while moderate to severe pain, or mild pain that is persistent or increasing despite non-opioid therapy, is best approached with an opioid type drug, with or without a non-opioid drug, and with or without an analgesic adjuvant [1].

The nonopioid analgesic drugs acetaminophen and NSAIDs have a well-established role in the treatment of cancer pain when used as single agents [2] In addition, when used in combination with opioids, these agents may provide analgesia that is additive to the opioid regimen, permitting a reduction in the opioid dose, with a consequent lessening of opioid-related side effects.

This topic review will cover the use of acetaminophen and NSAIDs in cancer pain management. The use of other adjuvant analgesics (coanalgesics) such as antidepressants, anticonvulsants, and glucocorticoids, an overview of assessment of cancer pain, a review of specific cancer pain syndromes, general principles of cancer pain management, the clinical use of opioid analgesics, an overview of risk management in patients treated with opioids, prevention and management of opioid side effects, and non-pharmacologic methods of cancer pain management are covered elsewhere (see appropriate topic reviews).

ACETAMINOPHEN

Acetaminophen has been used as monotherapy for mild pain. It is also a component of a variety of combination opioid products (acetaminophen plus codeine, hydrocodone, or oxycodone). When used in combination with an opioid to treat postoperative pain, acetaminophen has an opioid-sparing effect. (See "Nonopioid pharmacotherapy for acute pain in adults", section on 'Acetaminophen'.)

The treatment of opioid-naïve patients with moderate or severe cancer pain may be initiated with a combination product that includes an opioid plus acetaminophen (acetaminophen plus hydrocodone or oxycodone) or with a low-dose single-entity opioid. There is insufficient evidence to recommend one of these approaches over the other. If a patient initiates therapy with a single-entity opioid alone and experiences mild residual pain after the dose is adjusted, trial of acetaminophen, administered around-the-clock using fixed scheduled dosing, may be considered, particularly if the patient is very sensitive to opioid side effects.

If acetaminophen is administered around-the-clock, either through the use of a combination product or through coprescription of single-entity acetaminophen, and pain increases, a higher dose of acetaminophen should not be given unless the total daily dose is below the maximum safe dose. Usually, an alternative strategy, typically escalation of the opioid alone, is needed in this situation.

The evidence to support the benefit of acetaminophen in combination with an opioid in patients with moderate to severe pain is surprisingly limited [2-14]. However, most of the randomized trials that suggested no benefit were underpowered, and at least one trial suggests a small but clinically important additive effect in about one-third of patients despite the fact that one-half were taking an NSAID or glucocorticoid [10]. Nevertheless, a 2017 Cochrane review of three double-blind randomized trials comparing acetaminophen alone with placebo, or acetaminophen in combination with an opioid compared with the same dose of the opioid alone for at least five days' duration [9,11,12] concluded that risk of bias was high in all of these

studies, and that there was no high-quality evidence to support or refute the use of acetaminophen in patients with any severity of cancer pain [8]. On the other hand, a year 2019 network meta-analysis of therapeutics for chronic cancer pain concluded that the top-ranking drug classes for global efficacy included nonopioid analgesics, such as acetaminophen, as well as NSAIDs and opioids [2].

The analgesic mechanisms underlying the benefit of acetaminophen are poorly understood, but may involve inhibition of prostaglandin formation in the CNS, as well as other mechanisms [15-17]. In contrast to the NSAIDs, acetaminophen is not anti-inflammatory, at least when peroxidase levels are high (eg, with tissue damage, and/or inflammation in peripheral sites) [18].

Intravenous acetaminophen — Intravenous (IV) acetaminophen may be used in patients in whom oral or rectal administration is not an option; it is most commonly used in the perioperative setting. (See "Nonopioid pharmacotherapy for acute pain in adults", section on 'Acetaminophen'.)

IV acetaminophen has a more rapid and predictable onset of effect (5 to 10 minutes) and time to peak concentration (15 minutes) in most patients compared with rectal or oral administration (onset 10 to ≥60 minutes). The usual dose of IV acetaminophen for patients over 50 kg is 650 mg every four hours or 1000 mg every six hours, not to exceed 4 g per day.

A reduced dose of acetaminophen should be used for low-weight adults (body weight 33 to 50 kg) and in patients with mild or moderate hepatic insufficiency, chronic alcoholism, malnutrition, or dehydration. Patients with severe renal insufficiency (creatinine clearance ≤30 mL/min) may receive the usual dose, but not more often than once every six hours. Acetaminophen is contraindicated in patients with severe hepatic insufficiency or severe progressive liver disease.

Hepatic toxicity — The side effect profile of acetaminophen is exceedingly good, but there is a relatively narrow therapeutic window, and the main toxicity, hepatic injury, is a serious concern and can be life threatening. Acetaminophen-induced hepatotoxicity has been generally associated with doses >4 g/day [19-21]. Although doses up to 4 g/day are generally well tolerated, hepatotoxicity has been reported rarely at this dose limit [22,23].

In the United States, concerns about unintentional overdose have been rising. Given that there are no data to show that taking more than 325 mg of acetaminophen per dose unit provides additional benefit that outweighs the added risks for liver injury, in 2011, the US Food and Drug Administration (FDA) asked drug manufacturers to limit the strength of acetaminophen in prescription combination drug products to 325 mg per dose unit [24]. As of January 2014, all

prescription combination drug products with more than 325 mg of acetaminophen per tablet have been withdrawn from the market and are no longer available.

Government regulators have also suggested that the maximum single dose should be limited to 650 mg, that the maximal total daily dose should be limited to no more than 4 g/day (for five days or less) for adults, and that patients with significant liver disease or heavy alcohol use should be considered to have a relative contraindication to this drug [24,25]. Other risk factors for acetaminophen hepatotoxicity include older age, poor nutritional status, fasting/anorexia, and concurrent use of drugs that interact with acetaminophen metabolism (eg, St John's wort, phenobarbital) [17].

Notably, acetaminophen is widely used as an over-the-counter pain and fever medication, and it is often combined with other ingredients, such as cough and cold ingredients. Consumers are often unaware that many such products contain acetaminophen, making it easy to accidentally take too much acetaminophen.

In order to diminish the risk of severe liver damage:

- Health care providers should only prescribe combination products that contain 325 mg or less of acetaminophen per dose unit [25]. Patients taking combination drug products that contain acetaminophen must be educated to limit alcohol consumption while taking acetaminophen and to avoid unintentional overdose through the use of over-the-counter drug combinations that contain acetaminophen.

- The maximum acetaminophen dose should be limited to <4 g/day. Some experts, including the consensus-based National Comprehensive Cancer Network (NCCN) guidelines for management of adult cancer pain [26], recommend a lower maximum dose of 3 g/day in adults with normal liver function, particularly when used for longer durations (eg, >7 days) for pain. When calculating total daily dose, confirm that all sources (eg, prescription, over the counter, combinations) are included. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation".)

- Heavy alcohol use, malnutrition, fasting, low body weight, advanced age, febrile illness, select liver disease, and use of drugs that interact with acetaminophen metabolism may increase the risk of hepatotoxicity; a lower total daily dose (eg, 2 g/day) or avoidance may be preferred. (See "Management of pain in patients with advanced chronic liver disease or cirrhosis".)

NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

The NSAIDS are a diverse group of drugs (table 1) that presumably produce analgesia by inhibiting the enzyme cyclooxygenase (COX), and thereby reducing production of peripheral and central prostaglandins. There are two main isoforms of COX, a constitutive form (COX-1) that is active in tissues that require prostaglandins for physiologic function, and an inducible form (COX-2) that is produced in the setting of inflammation.

Each of the NSAIDs inhibits both COX-1 and COX-2, but with varying selectively for the two isoforms. Drugs that are relatively more selective for COX-2 have analgesic and anti-inflammatory properties, but are relatively less likely to produce side effects related to COX-1 inhibition, such as gastrointestinal (GI) toxicity. (See 'Side effects' below.)

A number of drugs were specifically developed as relatively selective COX-2 inhibitors in order to reduce the risk of GI toxicity. Studies confirmed that these COX-2 selective drugs had lower rates of GI side effects, ulceration and bleeding, as long as low-dose aspirin therapy was not undertaken concurrently. (See "Overview of COX-2 selective NSAIDs", section on 'Coadministration with low-dose aspirin'.)

Cardiovascular toxicity has been identified in patients treated with any of the NSAIDs, and epidemiologic and other research has suggested that the prothrombotic effect that presumably causes this toxicity is produced by relatively excessive inhibition of the COX-2 enzyme. Mostly as a result of these concerns, two COX-2 selective NSAIDs were taken off the market in the United States, and others have not been approved. Subsequent research has confirmed that there is large drug-specific variation in the risk of cardiovascular toxicity among both the COX-2 selective drugs and the non-selective COX-1/COX-2 inhibitors. Celecoxib, currently the only available NSAID labeled a selective COX-2 inhibitor in the US, appears to have a far lower risk than other drugs in this class; similarly, some of the non-selective drugs, such as naproxen and ibuprofen, appear to have relatively lower risk. (See "NSAIDs: Adverse cardiovascular effects".)

Efficacy — NSAIDS are effective analgesics for cancer pain when used as single agents or in combination with opioids [3,13,27]. There is slightly more evidence to support additive analgesic benefit from the combination of an NSAID plus an opioid than there is with combinations of acetaminophen plus an opioid [8,13,27]:

- A 2017 Cochrane review included 11 randomized trials comparing different NSAIDS (eight trials) or a step III opioid with or without an NSAID (three trials); there were no trials comparing an NSAID with placebo [8]. Initially moderate or severe pain was reduced to no worse than mild pain after one or two weeks in four studies (totaling 415 participants), with a range of estimates between 26 and 51 percent in individual studies. All of the studies were at high risk of bias for lack of blinding, incomplete outcomes data, or small

size. Common adverse events with NSAIDs were thirst/dry mouth (15 percent), loss of appetite (14 percent), somnolence, and dyspepsia (11 percent each). The authors concluded that there was no high-quality evidence to support or refute the benefit of NSAIDs, either alone or in combination with opioids, for any severity of cancer pain; there was very low-quality evidence that some patients with moderate to severe cancer pain can obtain substantial levels of benefit within one or two weeks.

- The lack of high-quality evidence regarding the analgesic efficacy of NSAIDs in cancer patients was reiterated in a year 2019 systematic review [27].

- On the other hand, a year 2019 network meta-analysis of therapeutics for chronic cancer pain concluded that NSAIDs were one of the top-ranking drug classes for global efficacy, in addition to nonopioid analgesics (eg, acetaminophen) and opioids [2].

- A 2021 systematic review of the effects of one NSAID (ketorolac) on opioid sparing in patients with chronic cancer pain evaluated nine studies employing heterogeneous methodologies; the data were insufficient to draw conclusions but the one included randomized controlled trial found a significant degree of morphine sparing (standard mean difference [SMD] -4.30 mg, 95% CI -5.36 to -3.25 mg) [28].

Based on clinical observations, NSAIDs may be especially useful in patients with bone pain or pain that is related to grossly inflammatory lesions. They are relatively less useful in patients who have neuropathic pain. (See "Cancer pain management: Role of adjuvant analgesics (coanalgesics)", section on 'Patients with neuropathic pain'.)

However, the utility of NSAIDs for cancer pain is limited by side effects and a "ceiling" dose for analgesia, above which additional dose increments fail to produce more relief.

Side effects — Side effects that may be associated with NSAIDs include the following (see "Nonselective NSAIDs: Overview of adverse effects"):

Cardiovascular toxicity — The risks of major cardiovascular events, such as myocardial infarction (MI), stroke, and death, appear to be increased to a similar degree by use of most nonselective NSAIDs at high dose, with the exception of naproxen, which might be safer than other nonselective NSAIDs [29,30], although this remains a controversial area [31]. In this meta-analysis, the estimated excess absolute risk of a major vascular event or death with use of diclofenac, a COX-2 inhibitor, and possibly ibuprofen was 2 events per 1000 persons per year in patients at low baseline cardiovascular risk, and 7 to 8 events per 1000 persons per year, including 2 fatal events, in patients at high baseline cardiovascular risk [29]. Naproxen has been the preferred nonselective NSAID when long-term use is needed in patients at increased risk for

cardiovascular disease, but not for those at high risk of gastrointestinal events [32]. (See "NSAIDs: Adverse cardiovascular effects".)

The prothrombotic effects caused by NSAIDs presumably occur at the time dosing is initiated; however, the risk of adverse outcomes is cumulative over time. Furthermore, risk may increase further when there are concomitant adverse effects on blood pressure. (See "NSAIDs and acetaminophen: Effects on blood pressure and hypertension".)

Gastrointestinal toxicity — NSAIDs produce both dyspepsia and gastroduodenal ulceration (peptic ulcer disease). The likelihood and severity seem to be less with COX-2-selective drugs than with ibuprofen and naproxen, at least over the short-term [29,32].

Pretreatment risk stratification can be helpful to estimate the risk of NSAID-induced GI toxicity and guide management of these patients. The American College of Gastroenterology published guidelines for prevention of NSAID-induced ulcers in 2009 [33]. These guidelines risk stratify patients into high, moderate, or low risk for GI complications of NSAID use based on the number of positive risk factors they have (see "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity"):

- A history of an ulcer or GI hemorrhage, which increases risk four- to fivefold
- Age >60, which increases risk five- to sixfold
- High (more than twice the customary) dose of an NSAID, which increases risk 10-fold
- Concurrent use of glucocorticoids, which increases risk four- to fivefold
- Concurrent use of anticoagulants, which increases risk up to 15-fold (see "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Mitigating bleeding risk' and "Risks and prevention of bleeding with oral anticoagulants")

High-risk patients were defined as having a history of a previous complicated ulcer (especially recent) or >2 other risk factors; the committee suggested avoiding NSAIDs in such patients. Low-risk patients have no risk factors. For moderate-risk patients, those with one to two risk factors, the committee recommended concomitant use of a gastroprotectant. (See 'Improving the therapeutic ratio: choice of drug, dose and use of gastroprotectants' below.)

The role of *H. pylori* infection in the development of peptic ulcer disease in patients treated with NSAIDs is uncertain. A 2018 systematic review included studies evaluating the outcomes associated with *H. pylori* infection among patients taking daily low-dose aspirin; based on seven case control studies, the authors concluded that infection approximately doubled the risk for upper gastrointestinal hemorrhage [34]. Some expert groups endorse testing for *H. pylori* for patients who are beginning NSAID therapy if they have a history of ulcer complications or a history of ulcer disease (non-bleeding), and treatment for those who are positive. (See "NSAIDs

(including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity" and "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity", section on 'Helicobacter pylori infection'.)

Bleeding — Most NSAIDs interfere with platelet aggregation; exceptions include the nonacetylated salicylate (eg, diflunisal, magnesium salicylate, and salsalate) and the selective COX-2 inhibitors. Despite its short half-life, aspirin irreversibly inhibits platelet aggregation for the lifetime of the platelet (four to seven days); the inhibitory effect of other NSAIDs lasts about two days. (See "Overview of COX-2 selective NSAIDs" and "Nonselective NSAIDs: Overview of adverse effects", section on 'Antiplatelet effects'.)

Nephrotoxicity — Reversible renal insufficiency due to renal vasoconstriction, acute interstitial nephritis, and a predisposition to acute tubular necrosis in patients with low renal perfusion have been associated with NSAID use. Prolonged NSAID use also can cause chronic nephropathy, which may be irreversible. (See "NSAIDs: Acute kidney injury".)

Hepatotoxicity — Hepatotoxicity can be seen with NSAIDs, even at recommended doses. The elevations in liver enzymes are generally mild and reversible with discontinuation of the NSAID. (See "Nonselective NSAIDs: Overview of adverse effects", section on 'Hepatic injury'.)

Indications and contraindications — A trial of an NSAID may be considered in any patient who has mild to moderate chronic cancer pain. However, the decision to offer treatment should consider the likelihood of benefit, the risk of adverse effects, and the cost and burden associated with prolonged treatment (see 'Side effects' above):

- Based on clinical observations, NSAIDs are especially useful in patients with bone pain or pain that is related to grossly inflammatory lesions, and relatively less useful in patients with neuropathic pain.

- Patients who are deemed at high risk for peptic ulcer disease or its complications as a result of advanced age, a history of peptic ulcer disease or prior NSAID gastroduodenopathy, advanced illness or bleeding diathesis, or concurrent corticosteroid use should be considered to have a relative contraindication to use of an NSAID. (See 'Gastrointestinal toxicity' above.)

- Given the likelihood that all NSAIDs have at least some prothrombotic effects, patients who have a strong history of cardiovascular disease or evidence of cancer-related hypercoagulability (eg, a history of venous thrombosis) also should be considered to have a relative contraindication to NSAID therapy. (See 'Cardiovascular toxicity' above.)

- All NSAIDs may cause serious nephrotoxicity, and preexisting renal disease (or strong predisposing factors, such as a diagnosis of multiple myeloma, or low perfusion states such as heart failure) represent contraindications to their use. NSAIDs should be prescribed with caution in patients with hypertension, renal insufficiency, or low renal perfusion states such as heart failure.

Improving the therapeutic ratio: choice of drug, dose and use of gastroprotectants — For patients who have none of these contraindications and are reasonable candidates for NSAID therapy, it may be possible to reduce risk further through drug or dose selection and the use of concomitant therapy such as gastroprotectants.

Although epidemiologic studies indicate the existence of substantial differences in risk across specific NSAIDs, there are few adequate comparative trials, and firm conclusions are not possible. Nevertheless, in general, GI risk correlates with anti-inflammatory activity, and those NSAIDs whose analgesic and anti-inflammatory doses are similar (eg, piroxicam and ketorolac) pose a greater risk, and should probably be avoided. In addition to celecoxib, limited data suggest that some other NSAIDs (ibuprofen, naproxen, nabumetone, and the nonacetylated salicylates such as salsalate) have a relatively lower risk of GI toxicity. Regardless of the drug selected, lower doses are associated with less risk than are higher doses.

Thus, to minimize the risk of ulcer and related adverse effects, a trial of celecoxib (with or without a loading dose, initially dosed at 100 mg twice daily, up to a maximum of 400 mg daily (table 1)) could be considered, or if this is unavailable, ineffective or poorly tolerated, ibuprofen, naproxen or one of the other relatively lower-risk NSAIDs. Taking the drug with food and/or antacids may also improve GI tolerance.

Pharmacologic approaches to preventing gastroduodenal toxicity include the concurrent use of a gastroprotectant (eg, a proton pump inhibitor [PPI] such as omeprazole, or the prostaglandin analogue misoprostol). A PPI is preferred over other preventive approaches because of their convenience and relatively good safety profile [35]. For patients over 60 who are receiving an NSAID, including celecoxib, we routinely coprescribe a PPI.

We suggest coadministration of a PPI in patients who need an NSAID and who qualify as having moderate risk for gastrointestinal complications, as suggested in the AGA guidelines. (See 'Gastrointestinal toxicity' above and "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

At least some data suggest that naproxen may have a lower risk of cardiovascular toxicity than other nonselective NSAIDs [36,37]. However, there are conflicting data on this issue. Nevertheless, selection of naproxen is reasonable in a patient who is otherwise eligible for a

trial of NSAID therapy if there is a relatively high concern about gastrointestinal or prothrombotic effects. (See "NSAIDs: Adverse cardiovascular effects".)

Because there is substantial variability in the response of individual patients to the various NSAIDs, the decision to try an NSAID may require several trials to identify the agent with the most favorable risk to benefit ratio. In addition to risk-related factors, there may be other important considerations as specific drugs are considered. For example, a past response to an NSAID may inform current drug selection. Pharmacokinetic considerations may also be important, in that an NSAID that can be given once daily (eg, nabumetone) or twice daily (many options) is usually better for fixed schedule, open-ended dosing. Cost and availability considerations may also be relevant considerations.

Regardless of the agent chosen, all patients receiving an NSAID should be evaluated periodically for occult fecal blood, changes in blood pressure, and effects on renal or hepatic function.

Intravenous NSAIDs — Some NSAIDs are available in an intravenous (IV) formulation. Ketorolac, ibuprofen, and meloxicam are the nonselective NSAIDs that are available for IV use in the United States. Diclofenac is available for IV use in other countries. These agents are most often used for treatment of perioperative pain in patients who cannot take oral NSAIDs. (See "Nonopioid pharmacotherapy for acute pain in adults", section on 'Nonsteroidal anti-inflammatory drugs'.)

The usual dose of ketorolac is 15 to 30 mg IV over 15 seconds. The usual dose of ibuprofen is 400 to 800 mg IV in 100 mL IV fluid over 30 minutes. The usual dose of IV meloxicam is 30 mg once daily administered over 15 seconds.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Palliative care" and "Society guideline links: Cancer pain".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Managing pain when you have cancer (The Basics)" and "Patient education: Acetaminophen poisoning (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Acetaminophen and NSAIDs are nonopioid analgesics that are frequently used in the treatment of mild to moderate cancer-related pain. Analgesia may be additive to that of opioids, permitting a reduction in the opioid dose, with a consequent lessening of opioid-related side effects. (See 'Introduction' above.)

- The use of combination products that include an opioid plus acetaminophen (acetaminophen plus codeine, hydrocodone, or oxycodone) is a reasonable alternative to low doses of a strong opioid alone for opioid-naive patients with moderate to severe cancer pain. In addition, for patients who begin therapy with an opioid alone, a trial of fixed-schedule dosing with acetaminophen may be considered in those who have mild residual pain, particularly if the patient is very sensitive to opioid side effects. However, severe liver damage may result from taking too much acetaminophen. When the maximum dose of acetaminophen is reached, an alternative strategy for pain control is needed. (See 'Hepatic toxicity' above.)

  Acetaminophen is also widely used as an over-the-counter pain and fever medication, and is often combined with other ingredients, such as cough and cold ingredients. Consumers are often unaware that many such products contain acetaminophen, making it easy to accidentally take too much acetaminophen. In order to diminish the risk of severe liver damage (see 'Acetaminophen' above):

  - Health care providers should only prescribe combination products that contain 325 mg or less of acetaminophen per dose unit. The maximum dose should be limited to 4

g/day with maximal single doses not to exceed 1000 mg. The maximum dose should be lower, ≤2 g/day, if the patient has known chronic liver disease.

- Patients taking combination drug products that contain acetaminophen must be educated to avoid heavy alcohol consumption while taking acetaminophen and to avoid use of over-the-counter drug combinations that contain acetaminophen.

- A trial of an NSAID is reasonable for a patient with mild to moderate cancer-related pain and no contraindication to the use of NSAIDs. Relative contraindications include a history of peptic ulcer disease or prior NSAID gastroduodenopathy, a bleeding diathesis, or concurrent corticosteroid use, strong history of cardiovascular disease, evidence of cancer-related hypercoagulability, or preexisting renal disease. Some expert groups endorse testing for *H. pylori* for patients who are beginning NSAID therapy if they have a history of ulcer complications or a history of ulcer disease (non-bleeding). (See 'Side effects' above and 'Indications and contraindications' above.)

- In the absence of a contraindication, we suggest a trial of an NSAID in the setting of bone pain or cancer-related pain that has an inflammatory component (**Grade 2B**). (See 'Efficacy' above.)

- Drugs of this class are less useful for neuropathic pain, and we suggest other therapeutic alternatives rather than NSAIDs in this setting (**Grade 2C**). (See 'Indications and contraindications' above and "Cancer pain management: Role of adjuvant analgesics (coanalgesics)", section on 'Patients with neuropathic pain'.)

- The choice of specific drug is empiric. NSAIDs that can be given once or twice daily are preferred (table 1). If there is a desire to minimize GI toxicity, we suggest celecoxib (if cardiovascular toxicity is not a concern) or one of the nonselective NSAIDs that have a relatively lower risk of GI toxicity (eg, ibuprofen, naproxen, nabumetone, or salsalate) (**Grade 2C**). (See 'Improving the therapeutic ratio: choice of drug, dose and use of gastroprotectants' above.)

- If there is a desire to minimize the risk of cardiovascular toxicity, naproxen is a reasonable choice, as it may have a lower risk of cardiovascular toxicity than other nonselective NSAIDs or celecoxib; however, the risk of GI toxicity may be higher, at least higher than with celecoxib. (See 'Cardiovascular toxicity' above.).

- For all patients taking an NSAID, we suggest using the lowest dose possible, and taking each dose with food and/or antacids.

We suggest coadministration of a proton pump inhibitor (PPI) in patients who require an NSAID and are at moderate risk for GI toxicity (**Grade 2B**). This includes patients who: have a history of upper GI bleeding, are receiving a concomitant anticoagulation, and have more than one risk factor for complications, including age 60 or more, dyspepsia or reflux symptoms. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

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GRAPHICS

Nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (paracetamol): Usual oral dosing for adults with pain or inflammation and selected characteristics

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Nonselective NSAIDs*			
Acetic acids			
Diclofenac¶	50 mg every 8 to 12 hours	150 mg For rheumatoid arthritis, labeling in United States permits up to 200 mg Approved maximum in Canada is 100 mg	▪ Dosing for free-acid preparation differs from doses listed here for sodium or potassium salts; refer to UpToDate Lexidrug monograph
Etodolac	200 to 400 mg every 6 to 8 hours	1000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at lower total daily dose of 600 to 800 mg
Indomethacin	25 to 50 mg every 8 to 12 hours	150 mg For rheumatologic conditions, labeling in United States permits up to 200 mg	▪ Used for treatment of acute gout and certain types of headache ▪ Potent inhibitory effects on kidney prostaglandin synthesis ▪ More frequently associated with CNS side effects (eg, headache, altered mental status) compared with other NSAIDs
Sulindac	150 to 200 mg every 12 hours	400 mg	▪ Rarely used ▪ More frequently associated with hepatic inflammation than other NSAIDs ▪ Metabolites implicated in the formation of renal calculi

Fenamates			
Meclofenamate (meclofenamic acid)	50 mg every 4 to 6 hours or 100 mg 3 times daily up to 6 days for dysmenorrhea	400 mg	▪ Used for treatment of dysmenorrhea ▪ Relatively higher incidence of GI side effects
Mefenamic acid	250 mg every 6 hours or 500 mg 3 times daily	1000 mg For dysmenorrhea, up to 1500 mg	▪ Used for treatment of dysmenorrhea; not indicated for treatment of chronic pain or inflammation ▪ Do not exceed 3 days (dysmenorrhea) to 7 days (acute pain) of use ▪ Less potent antiinflammatory effec
Nonacidic			
Nabumetone	1000 mg once to twice daily	2000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at daily dose ≤1000 mg
Oxicams			
Meloxicam[Δ]	7.5 to 15 mg once daily (conventional tablet, oral suspension) 5 to 10 mg once daily (capsule)	15 mg (conventional tablet, oral suspension) 10 mg (capsule)	▪ Long duration of effect; relatively slow onset ▪ Relative COX-2 selectivity and minimal effect on platelet function at lower daily dose of 7.5 mg
Piroxicam	10 to 20 mg once daily	20 mg	▪ Long-acting alternative for treatment of chronic pain and inflammation poorly responsive to other NSAIDs ▪ Prescribing generally limited to specialists with experience in treatment of chronic pain and inflammation
Propionic acids			
Fenoprofen	200 mg every 4 to 6 hours or 400 to 600 mg every 6 to 8 hours	3200 mg	▪ More frequently associated with acute interstitial nephritis and nephrotic syndrome[1]

Flurbiprofen	50 mg every 6 hours or 100 mg every 8 to 12 hours	300 mg	
Ibuprofen[Δ]	400 mg every 4 to 6 hours or 600 to 800 mg every 6 to 8 hours	3200 mg (acute), 2400 mg (chronic)	▪ Shorter-acting alternative to naproxen; useful in patients withou cardiovascular risks
Ketoprofen	50 mg every 6 hours or 75 mg every 8 hours	300 mg	
Naproxen	Base: 250 to 500 mg every 12 hours or 250 mg every 6 to 8 hours	Base: 1250 mg (acute); 1000 mg (chronic); may increase to 1500 mg during a disease flare	▪ Often preferred by UpToDate for treatment of acute or chronic pain and inflammation in patients without relevant comorbidities or risks ▪ Higher dose (eg, 500 mg base twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs;[2] refer to UpToDate topic review of cardiovascular effects of nonselective NSAIDs ▪ Naproxen sodium has a faster onse than naproxen base
	Naproxen sodium: 275 to 550 mg every 12 hours or 275 mg every 6 to 8 hours	Naproxen sodium: 1375 mg (acute); 1100 mg (chronic); may increase to 1650 mg during a disease flare	
Oxaprozin	1200 mg once daily	1200 mg or 1800 mg depending on body weight (refer to UpToDate Lexidrug monograph)	▪ Prolonged half-life (41 to 55 hours); requires several days of treatment to reach full effect
Salicylate (acetylated)			
Aspirin	325 to 1000 mg every 4 to 6 hours	4000 mg	▪ Not commonly used for chronic pain and inflammation ▪ High daily doses have been used as antiinflammatory therapy; such use is limited by toxicity ▪ Irreversibly inhibits platelet functio ▪ Refer to appropriate UpToDate clinical topics and drug monograph for other uses
Salicylates (nonacetylated)			

Diflunisal	500 mg every 8 to 12 hours	1500 mg	▪ No significant effect on platelet function at usual doses ▪ Relatively lower GI bleeding risk than other nonselective NSAIDs at usual doses ▪ May be tolerated at lower daily doses by adults with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis); refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Magnesium salicylate	1160 mg every 6 hours	4640 mg	
Salsalate	1000 mg every 8 to 12 hours or 1500 mg every 12 hours	3000 mg	
COX-2 selective NSAIDs			
Celecoxib	200 mg daily or 100 mg every 12 hours	400 mg	▪ Less risk of GI toxicity relative to nonselective NSAIDs; benefit negated by low-dose aspirin, which may require concurrent gastroprotection ▪ No effect on platelet function ▪ Cardiovascular and kidney risks are dose-related and may be similar to nonselective NSAIDs ▪ May be tolerated by patients with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis) who cannot take other NSAIDs; refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Etoricoxib (not available in the United States)	30 to 60 mg once daily	60 mg (chronic pain and inflammation) 120 mg (acute pain for up to 8 days)	▪ May be associated with more frequent and severe dose-related cardiovascular effects (eg, hypertension) ▪ Other risks and benefits similar to celecoxib
Non-NSAID analgesic			
Acetaminophen (paracetamol)[Δ]	325 to 650 mg every 4 to 6 hours or 1000 mg every 6 hours up to 3	3000 mg 4000 mg in selected medically supervised patients	▪ Effective for noninflammatory pain; may decrease opioid requirements ▪ Doses ≤2000 mg per day do not appear to increase risk of serious G complications[3]

	times daily	Avoid or use a lower total daily dose (maximum 2000 mg) in older adults, patients at increased risk for hepatotoxicity (eg, regular alcohol use, malnourished), or patients with organ dysfunction	▪ Does not alter platelet function ▪ Can cause hepatotoxicity in chronic or acute overdose ▪ To avoid overdose, warn patients about acetaminophen content in combination prescription (eg, oxycodone-acetaminophen) and nonprescription (OTC) preparations

NSAIDs are useful for treatment of acute and chronic painful and inflammatory conditions and may reduce opioid requirements. The indications for use of NSAIDs in specific disorders, adverse effects, and toxicities are presented in the relevant UpToDate topics including reviews of NSAID-associated adverse cardiovascular effects, gastroduodenal toxicity, acute kidney injury, etc.

UpToDate contributors generally avoid use of NSAIDs, or use them with particular caution and at reduced doses, in older adults and patients (regardless of age) with existing or increased risk for cardiovascular, GI, or kidney disease. Concurrent gastroprotection (eg, a proton pump inhibitor) may be warranted. For information on gastroprotective strategies, including use of selective COX-2 inhibitors and other options, refer to the UpToDate topic reviews of COX-2 selective NSAIDs and NSAIDs (including aspirin) and primary prevention of gastroduodenal toxicity.

Short- to moderate-acting NSAIDs (eg, naproxen, ibuprofen) are preferred for most patients. Use the lowest effective dose for the shortest duration of time. For chronic inflammatory conditions, a trial of ≥2 weeks is advised to assess full efficacy. For patients who experience an inadequate response to an NSAID of 1 class, it is reasonable to substitute an NSAID of another class.

Dosing in this table is for immediate-release preparations in patients with normal organ (eg, kidney) function. For treatment of acute pain, a loading dose of some NSAIDs may be used; refer to UpToDate Lexidrug monographs.

Drug interactions may be determined by use of the drug interactions program included within UpToDate.

AERD: aspirin-exacerbated respiratory disease; CNS: central nervous system; COX-2: cyclooxygenase, isoform 2; GI: gastrointestinal; OTC: over the counter.

* Nonselective NSAIDs reversibly inhibit platelet function, with some exceptions noted above.

¶ Also available as a topical agent.

Δ Also available for parenteral use.

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Data from: UpToDate Lexidrug. More information available at https://online.lexi.com/.

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Russell K Portenoy, MD No relevant financial relationship(s) with ineligible companies to disclose. **Ebtesam Ahmed, PharmD, MS** No relevant financial relationship(s) with ineligible companies to disclose. **Yair Y Keilson, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Janet Abrahm, MD** Other Financial Interest: Johns Hopkins University Press [Pain, palliative care, ethics, bone disease in cancer patients]. All of the relevant financial relationships listed have been mitigated. **Melinda Yushak, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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