Cancer pain management: Role of adjuvant analgesics (coanalgesics)

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

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Feb 2024.**
This topic last updated: **Dec 16, 2022.**

INTRODUCTION

Opioid therapy is the first-line approach for moderate or severe chronic pain in populations with active cancer. If opioid therapy by itself yields a good outcome (satisfactory analgesia, tolerable side effects, and treatment adherence) additional analgesic interventions are not needed. Should the patient demonstrate a poor response to the opioid, however, therapy must be changed. This common scenario may be addressed in many ways, among which is the addition of another analgesic drug.

In some cases, the use of a nonopioid analgesic, such as acetaminophen (paracetamol) or a nonsteroidal anti-inflammatory drug (NSAID), is appropriate and sufficient. In others, significant benefit may be obtained by the addition of a so-called "adjuvant analgesic" or coanalgesic. This topic review will cover the use of adjuvant analgesics in cancer pain management. Assessment of cancer pain, a review of specific cancer pain syndromes, clinical use and side effects of opioid analgesics, use of acetaminophen and NSAIDs in patients with cancer pain, and nonpharmacologic methods of cancer pain management are covered elsewhere. (See "Cancer pain management: General principles and risk management for patients receiving opioids", section on 'General principles of pain management' and "Cancer pain management with opioids: Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal anti-inflammatory drugs".)

DEFINITION OF AN ADJUVANT ANALGESIC

The term "adjuvant analgesic" originally referred to a small number of drugs that were approved and marketed for indications other than pain but were found to be potentially useful as analgesics in patients receiving opioid therapy. Over the past three decades, the number and types of these nontraditional analgesics has increased dramatically [1]. Some are now commonly used as single entity treatments for chronic pain and several have been approved for pain indications in the United States and elsewhere. As such, the term "adjuvant analgesic" as used originally, is a misnomer. However, a simple definition that applies in all settings states that an "adjuvant analgesic" is a drug that has a clinical use other than pain but is used as an analgesic in selected circumstances.

In the context of cancer pain, however, the designation of adjuvant analgesic is still apt given the typical co-administration of an adjuvant drug with an opioid, and the term "coanalgesic" is synonymous.

Integration into cancer pain management

Timing of an adjuvant analgesic — There are no published data that inform the decision about the timing of adjuvant analgesic therapy in patients with cancer-related pain and this is a matter of clinical judgment. We base our decision, in part, on whether the patient has active cancer or is a cancer survivor. In contrast to patients with active cancer, in whom adjuvant analgesics may be added to opioids if chronic pain is poorly responsive to opioids, cancer survivors with chronic (typically neuropathic) pain usually receive an initial trial of an adjuvant analgesics, and opioids are only considered on a case-by-case basis, after other therapeutic trials have been ineffective. This more limited role reflects concern about the ongoing risks associated with opioid drugs and the need for careful long-term management of adverse effects related to both drug toxicities and abuse. (See 'General principles' below.)

Adjuvant analgesics are often considered for treatment of chronic mild, moderate, or severe cancer pain when a patient is poorly responsive to opioids (ie, inability to titrate the opioid to a dose that maintains a favorable balance between analgesia and side effects). The addition of an adjuvant analgesic is one approach among many that may be considered for such patients [2]. Alternative approaches may include rotation to a different opioid, more aggressive treatment of the side effect that is limiting dose escalation, or a trial of an intervention (such as a nerve block) or other nonpharmacologic treatment. (See "Cancer pain management with opioids: Optimizing analgesia", section on 'Dose titration' and "Prevention and management of side effects in patients receiving opioids for chronic pain".)

Although the role of the adjuvant analgesics in addressing pain that has not been opioid responsive suggests that these drugs are typically tried after the opioid regimen has been optimized, there is variability in the timing of adjuvant analgesic therapy in clinical practice. In a setting where a patient may benefit from a nonanalgesic effect of the adjuvant drug (eg, mood enhancement from an analgesic antidepressant or a reduction in skeletal-related events from a bisphosphonate), early administration of the adjuvant analgesic, before the full effect of an opioid has been ascertained, is reasonable and may in fact be preferable. On the other hand, if the primary outcome of interest is analgesia (eg, the use of a gabapentin for the treatment of cancer-related neuropathic pain), some experts believe that treatment should be delayed until efforts have been made to optimize opioid therapy, while others believe that early use, in tandem with cautious opioid titration, produces better outcomes associated with an opioid-sparing effect. The potential benefits associated with delaying the trial of an adjuvant analgesic in this setting includes ensuring that the drug is needed, reducing the risk of additive toxicity by sequencing drug titration efforts, and limiting confusion as to the source of an adverse drug effect should one arise. This approach of delaying initiation of the adjuvant analgesic gains limited support from a systematic review [3].

Available agents and dose ranges — Based upon conventional practice, the categories of available agents used commonly for cancer pain include (table 1):

- Drugs potentially useful for any type of pain (multipurpose analgesics)
- Drugs used for treatment of neuropathic pain
- Drugs used for bone pain
- Drugs used for pain and other symptoms in the setting of bowel obstruction

With just a few exceptions, recommendations for multipurpose analgesics and the drugs used for neuropathic pain in the cancer population are based upon clinical experience and data derived from studies of populations with chronic noncancer pain, particularly populations with neuropathic pain [1]. This information is evolving as new trials are conducted, and as clinical experience expands with newer agents.

Commonly used adjuvant analgesics are described in the table (table 2). For most drugs, effective dose ranges vary and many require dose titration, a gradual incrementing of the dose from a relatively low starting dose until the analgesic effect is achieved, adverse effects become unmanageable, or the conventional maximal dose is achieved.

ANY TYPE OF CHRONIC PAIN: MULTIPURPOSE ANALGESICS

Some drug classes, including the glucocorticoids, antidepressants, alpha-2 adrenergic agonists, cannabinoids, some topical therapies, and botulinum toxin have been studied in diverse types of chronic pain, and the available data suggest the potential for efficacy in multiple types of chronic pain, including cancer pain. These drugs may therefore be considered multipurpose analgesics.

Glucocorticoids

Indications — Recommendations for use of glucocorticoids in the treatment of cancer-related pain are not evidence-based due to limitations in the existing literature. Randomized trials that have been conducted to assess the analgesic properties of glucocorticoids in cancer patients have been small and have produced mixed results [4-11]. A 2015 systematic review of six randomized trials found that glucocorticoid therapy resulted in modestly less pain compared with control treatment (placebo or usual treatment/supportive care) at one week (mean difference on a 1 to 10 numeric pain scale of 0.84 [95% CI 1.38-0.30]) [12]. The quality of the evidence was weak and the authors concluded that additional trials are needed to evaluate the safety and effectiveness of glucocorticoids for management of cancer pain in adults. (See "Assessment of cancer pain", section on 'Nociceptive pain' and "Management of vasogenic edema in patients with primary and metastatic brain tumors" and "Treatment and prognosis of neoplastic epidural spinal cord compression".)

Notwithstanding this limited evidence, there is a large clinical experience suggesting that glucocorticoids can be useful in the treatment of a variety of types of cancer pain, including neuropathic and bone pain, pain associated with stretch of an organ capsule caused by a space-occupying lesion (eg, within the liver or kidney) or duct obstruction, pain from malignant bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. Using these drugs for cancer pain, however, always must consider the potential for toxicity associated with long-term administration, particularly at higher doses. Treatment for just several weeks may cause myopathy, immunocompromise, glucose intolerance, psychotomimetic effects, and hypoadrenalism. (See "Major adverse effects of systemic glucocorticoids".)

Because of this potential for toxicity, a careful risk-to-benefit analysis is warranted whenever a glucocorticoid is being considered for pain management. This analysis should weigh the availability of other treatments and the planned duration of treatment, the presence of other symptoms, the treatment context, and the patient's life expectancy. As examples:

- In the context of advanced illness and a very short prognosis (ie, days to weeks), some experts favor a trial of a glucocorticoid drug at a relatively low dose to address pain and

other common symptoms, such as nausea, fatigue, or dysphoria. This treatment usually is continued until the death of the patient.

- In other contexts, such as severe neuropathic pain in a patient with longer life expectancy, the risks of prolonged glucocorticoid treatment are usually considered too substantial to consider open-ended therapy. Instead, short-term treatment (ie, a "glucocorticoid pulse") is a reasonable option. As an example, two weeks of a gradually tapering regimen may be useful for patients with severe neuropathic pain to promote pain control while a different neuropathic agent (eg, pregabalin) is titrated to levels that provide pain relief. (See 'Choice of agent and dose' below.)

The use of glucocorticoids for specific types of cancer-related pain, including pain from bone metastases, and the pain associated with malignant bowel obstruction, are discussed below. (See 'Patients with bone pain' below and 'Patients with malignant bowel obstruction' below.)

Choice of agent and dose — Dexamethasone is usually preferred for the management of cancer-related pain, presumably because of its long half-life and relatively low mineralocorticoid effects (table 3). However, there is no empiric evidence that this drug is either safer or more effective in the cancer population than any other glucocorticoid. Prednisone and methylprednisolone are acceptable alternatives. (See "Overview of the pharmacologic use of glucocorticoids", section on 'Choosing a glucocorticoid regimen'.)

The dose and frequency should be selected based on the cause of pain, and its severity. For those experts who favor a trial of low-dose glucocorticoid for pain and other symptoms in the context of advanced cancer and short prognosis, a typical regimen, based on clinical experience, is prednisone 5mg once or twice daily or dexamethasone 0.75 to 1.5 mg once or twice daily.

There are some situations for which a brief regimen of higher-dose glucocorticoids might be appropriate. When short-term therapy (a "glucocorticoid pulse") is considered (eg, when a patient has a "pain crisis" with escalating pain and distress that do not respond well to an initial opioid therapy), a loading bolus may be used. In the past, the size of the loading bolus and the initial doses that follow were adapted from an approach used to manage acute and emerging epidural spinal cord compression (ESCC; including cauda equina syndrome). This approach, which included a dexamethasone loading dose as high as 96 mg followed by a rapid taper beginning at 24 mg four times daily, was believed to yield prompt pain relief and potentially better outcomes after treatment of the tumor. More recently, however, this approach to ESCC has been questioned because good evidence of benefit (particularly a favorable risk-to-benefit ratio) is lacking [13]. More recent guidelines endorse a lower dose glucocorticoid regimen

(dexamethasone 10 mg loading dose followed by 4 to 6 mg four times daily) in this setting [14]. (See "Treatment and prognosis of neoplastic epidural spinal cord compression", section on 'Glucocorticoids'.)

Given this changing perspective, some experts would still consider a higher-dose glucocorticoid regimen when managing patients with "pain crisis" who have not experienced rapid relief following opioid administration, but the interpretation of "high-dose" has become more conservative. When pain is severe and escalating despite opioid treatment, and patient distress is very high, treatment with a regimen of a test dose of 8 to 10 mg dexamethasone, to determine if the pain is steroid responsive, can be used. If there is a dramatic response, then 4 mg bid or 8 mg daily can be tried, and the dose down-titrated to the lowest dose that maintains pain relief while other analgesic treatments are added, if indicated.

Analgesic antidepressants

Indications — For a patient with chronic cancer pain that is poorly responsive to opioid therapy who also has a depressed mood, we suggest an early trial of an analgesic antidepressant rather than a different adjuvant analgesic.

Antidepressants have been widely studied in populations with chronic pain from a variety of conditions, and several meta-analyses have concluded that these drugs act as multipurpose analgesics and are effective for a wide range of pain conditions, including low back pain, various types of neuropathic pain, and fibromyalgia [1,15-22]. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Antidepressants'.)

Although very few of these studies have included cancer patients, the utility of these drugs for cancer pain is assumed and they are usually considered for patients with neuropathic pain that has not promptly responded to an opioid. However, given the range of their potential analgesic efficacy, they also could be considered for any type of chronic cancer pain that has not responded adequately to opioid therapy. (See 'Patients with neuropathic pain' below and "Assessment of cancer pain", section on 'Neuropathic pain'.)

Mechanism of analgesic effect — Antidepressants function as primary analgesics. Although pain reduction may be enhanced if there is a positive mood effect, analgesia is not dependent on mood elevation, and pain can be improved in euthymic patients. An early trial when pain is accompanied by depressed mood is appropriate in the hope of achieving a separate and positive effect on mood.

The antidepressant's primary analgesic mode of action is thought to be related to the enhanced availability of monoamines at synapses within neural pathways that are part of a descending

pain modulating system. Inhibition of norepinephrine reuptake appears to be the most important mode of action, but serotonergic and dopaminergic effects also may play a role in analgesia [23].

Selection of agent and dose — Given the more favorable side effect profile over tricyclic antidepressants (TCAs), among patients with serious medical illness, such as those with cancer, we consider a serotonin-norepinephrine reuptake inhibitor (SNRI; usually duloxetine) to be the first-line analgesic antidepressant, followed by a secondary TCA (usually desipramine). Given its activating effect, a trial of bupropion is reasonable if cancer pain is complicated by fatigue or somnolence, even though the evidence of analgesic efficacy is weak. Bupropion should be avoided in patients at risk for seizures.

Antidepressants comprise several subclasses and numerous drugs (table 1). Analgesic efficacy is best established for some of the TCA compounds [24-26] and the SNRIs [26-30] (although benefit from venlafaxine is debated [31]). There is minimal evidence of analgesic efficacy with the serotonin-selective reuptake inhibitors (SSRIs) [32,33]. Benefit has also been suggested for bupropion (a dopamine reuptake inhibitor) in patients with neuropathic pain, although the evidence is not robust [34,35].

The side effect profile of SNRIs (which includes nausea, sexual dysfunction, and somnolence or mental clouding) is more favorable relative to desipramine and nortriptyline, although there is a great deal of interindividual variation [36]. The SNRIs include duloxetine, milnacipran, venlafaxine, and desvenlafaxine. Evidence of analgesic effects is best established for duloxetine [28-30,37]. A five-week randomized trial of duloxetine in patients with chemotherapy-induced painful peripheral neuropathy associated with taxanes or platinum agents found that the drug was analgesic at a dose of 30 to 60 mg [37]. There are no analgesic trials comparing different drugs within the SNRI class. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine'.)

The TCAs include tertiary amine compounds, such as amitriptyline, and secondary amine compounds, such as nortriptyline and desipramine. The secondary amine drugs, which are more selective at noradrenergic reuptake sites, have a more favorable side effect profile than amitriptyline [36]. As a result, when a TCA is chosen in a medically ill patient, desipramine or nortriptyline is usually preferred. All of the TCAs are relatively contraindicated in patients with serious heart disease, severe prostatic hypertrophy, and narrow-angle glaucoma. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Side effects'.)

Given the potential for a dose-response relationship for pain [24] and a desire to avoid initial toxicity, all of the analgesic antidepressants should be started at a relatively low initial dose

(table 2). The dose may be increased in steps until benefit occurs, side effects supervene, or the conventional maximal dose has been reached. For the SNRIs, dose titration typically involves one or two increments; for the TCAs, many steps may be taken to explore the potential therapeutic range (dose or serum level, if this is measured). The starting dose for a trial of desipramine, for example, is 10 to 25 mg at night. The dose should be increased no more quickly than every few days in the absence of satisfactory relief or side effects, and the maximum dose may be 150 to 300 mg at night. Analgesia typically appears within a week of starting a dose (developing more rapidly than the antidepressant effects) and most patients who experience pain relief respond at a dose between 50 and 150 mg per day.

When relatively high doses of the TCA antidepressants are used (ie, above 100 mg per day), the plasma drug concentration and an electrocardiogram should be monitored. TCAs can prolong the QTc interval and predispose to cardiac arrhythmias, and should be used cautiously when a patient has known heart disease or is receiving other drugs (including methadone) that can prolong the QTc interval.

Unlike the tricyclics, duloxetine and bupropion do not prolong the QTc interval. However, gastrointestinal side effects (including nausea, dry mouth, and constipation) are common with duloxetine, and bupropion causes jitteriness or headache as relatively common initial side effects.

Discontinuation — It is always preferable to taper the antidepressants before discontinuing them if treatment has been given for more than several weeks, particularly at higher doses. Discontinuation symptoms may occur with all antidepressants and have been best described for both SNRIs and SSRIs. The antidepressant discontinuation syndrome caused by these drugs may include flu-like symptoms and signs, and psychiatric phenomena [38]. (See "Discontinuing antidepressant medications in adults", section on 'Discontinuation syndrome'.)

Alpha-2 adrenergic agonists — A trial of tizanidine, an alpha-2 adrenergic agonist, is an option for patients who have opioid-refractory chronic pain if other adjuvant analgesics have not helped. Patients who are hemodynamically unstable or predisposed to hypotension (eg, by autonomic neuropathy, intravascular volume depletion, or concurrent therapy with potent hypotensive agents) are not appropriate candidates. Like other centrally-acting drugs with prominent sedative effects, it must be used cautiously in patients with acute or chronic encephalopathy of any cause.

The analgesic effects produced by the alpha-2 adrenergic agonists, including clonidine, tizanidine, and dexmedetomidine, have been demonstrated in both animal and human studies. Clonidine may be analgesic when administered orally, transdermally, or intraspinally [39-41];

most studies in cancer-related pain have involved neuraxial administration in conjunction with an opioid. (See "Interventional therapies for chronic pain".)

Although there is less published evidence of analgesic efficacy for both tizanidine, an oral drug approved as an antispasticity agent [42], and the parenteral drug dexmedetomidine [43,44], it is reasonable to consider all the alpha-2-adrenergic agonists as multipurpose analgesics. These effects presumably relate to activation of monoamine-dependent endogenous pain modulating pathways in the spinal cord and brain.

Alpha-2 agonists often produce somnolence and dry mouth and may cause hypotension, which is usually orthostatic. Medically ill patients often are predisposed to these toxicities, and based on clinical experience, these drugs usually are considered as second-line therapies for chronic pain that has not responded to trials of other adjuvant analgesics. Tizanidine has less hypotensive effect than clonidine and usually is considered first when pain is the target symptom [42,45,46]. Dosing with tizanidine may be initiated just at bedtime in an effort to provide hypnotic effects (table 2). If the drug is tolerated, dose escalation may proceed using two divided doses per day.

Cannabis and cannabinoids

Indications and benefit — A trial of non-inhaled medical cannabis or a cannabinoid pharmaceutical can be offered to patients with advanced cancer who have pain that has not adequately responded to opioids or other adjuvant analgesics. However, these agents, which may be considered multipurpose analgesics, appear to have limited analgesic efficacy and relatively high side effect liability, and also may raise concerns among patients or families related to the history of cannabis as a drug of abuse. Patients who place a relatively high value on small improvements in pain intensity, physical functioning, and sleep quality, and who have a willingness to accept a small to modest risk of harms, usually tolerable and self-limited, may seek a therapeutic trial, while those who place a greater value on avoiding treatment-related toxicity may decline.

"Marijuana," "medical marijuana," and "cannabis" refer to naturally grown plant materials that are not regulated by the US Food and Drug Administration (FDA) and are procured by patients from legal marijuana dispensaries or street suppliers. The primary psychoactive ingredient is tetrahydrocannabinol (THC).

The term "cannabinoids" refers to compounds derived from the cannabis plant, which contains more than 60 cannabinoids. Some of these compounds have pharmacologic effects, presumably mimicking the effects of endogenous cannabinoid compounds (the endocannabinoids) interacting with specific receptors in the nervous system and other tissues.

Although concern about the abuse potential of cannabinoid drugs has slowed their development (see "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects"), several cannabinoid-type drugs are commercially available, and others are under study:

- The only United States approved cannabinoid (dronabinol) is approved only for chemotherapy-induced nausea and vomiting; a second oral agent, nabilone, is available in Canada and the United Kingdom, but was discontinued in the United States in 2019.

- An oromucosal spray containing THC plus cannabidiol (CBD; and smaller concentrations of other compounds), called nabiximols (Sativex), is approved in more than 20 countries (but not in the United States) for treatment of spasticity related to multiple sclerosis. In Canada, the drug had also been approved as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain, but this approval was withdrawn in January 2020 because of a lack of supporting data [47]. (See "Symptom management of multiple sclerosis in adults", section on 'Cannabinoids'.)

Although the evidence is limited and conflicting, there are data from controlled trials that suggest analgesic efficacy for cannabinoid drugs, as well as smoked cannabis [48-54]. Few studies have been conducted in cancer patients [51,55-57]. However, based on these data, the cannabinoids may be considered multipurpose analgesics for refractory pain in populations with advanced illness. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Cannabis and cannabinoids'.)

Multiple meta-analyses have been conducted on the analgesic effects of cannabis and cannabinoids:

- Two early systematic reviews and two meta-analyses evaluating randomized trials of cannabis and cannabinoids found some evidence of efficacy for chronic pain, especially neuropathic pain [58-61]. However, all included trials studying different formulations in varied patient populations, and most of the trials included patients with neuropathic pain; very few were conducted in cancer patients. Not surprisingly, the results have been variable, with most concluding that cannabis might alleviate neuropathic pain in some patients (low-quality evidence) but there was insufficient evidence for other types of chronic pain, including pain related to cancer.

- A later meta-analysis of five randomized controlled trials (n = 1442 participants, five trials studying nabiximols [56,57,62], and a sixth comparing THC or THC/CBD versus placebo [51]) in patients with cancer, all judged to be at low risk of bias, concluded that there was

no difference between cannabinoids and placebo for the difference in the change in average numeric rating scale pain scores (mean difference -2.1, 95% CI -0.48 to 0.07) [63]. Cannabinoids had a higher risk of adverse events, especially somnolence (odds ratio [OR] 2.69, 95% CI 1.54-4.71) and dizziness (OR 1.58, 95% CI 0.99-2.51).

- Most recently, a series of four linked systematic reviews summarizing the current body of evidence for benefits and harms, as well as patient values and preferences regarding oral medical cannabis or cannabinoids for chronic pain (both cancer- and noncancer-related) [64-67] came to the following conclusions:

  - Non-inhaled medical cannabis or cannabinoids results in a small to very small improvement in pain relief, physical functioning, and sleep quality among patients with chronic pain [64]. Compared with placebo, non-inhaled medical cannabis results in a small increase in the proportion of patients experiencing at least the minimally important difference (MID) of 1 cm on a 10 cm visual analog scale (VAS) for pain, modelled risk difference of 10 percent (95% CI 5-15 percent) based on a weighted mean difference (WMD) in the VAS from baseline of -0.50 (95% CI -0.75 to -0.25, moderate certainty of evidence) [64]. Four of the 32 randomized trials included in this analysis enrolled patients with cancer-related pain, and all used nabiximols as the experimental group. Benefits were less certain in cancer-related pain (WMD -0.10, 95% CI -0.28 to 0.09) than in noncancer pain (WMD -0.63, 95% CI -0.96 to -0.29). The amount of heterogeneity between studies was higher in the noncancer setting (75 percent) as compared with chronic cancer-related pain (27 percent).

    Non-inhaled medical cannabis also resulted in a very small improvement in physical functioning (4 percent modelled risk difference (0.1 to 8 percent) for achieving at least the MID of 10 points on a 100 point SF-36 physical functioning scale, WMD 1.67 points (0.03 to 3.31 points), high certainty of evidence), and a small improvement in sleep quality (6 percent modelled risk difference [2 to 9 percent] for achieving at least the MID of 1 cm on a 10 VAS sloop quality scale, WMD -0.35, 95% CI -0.55 to -0.14, high certainty of evidence).

    There was moderate certainty of evidence that non-inhaled cannabis probably results in a small increased risk of transient cognitive impairment, drowsiness, impaired attention, and nausea; and high-certainty evidence showing a greater risk of dizziness.

  - In a separate analysis, there was very low-certainty evidence that adverse events are common among people living with chronic pain who use medical cannabis or cannabinoids, but few patients experience serious adverse events [67].

- Another analysis concluded that there is low to very low certainty evidence that values towards medical cannabis among people living with chronic pain are highly variable, and high to moderate certainty evidence that patient's use of medical cannabis for chronic pain was influenced by both positive (eg, support from friends and family) and negative social factors (eg, stigma surrounding cannabis use) [65]. Many valued the effectiveness of medical cannabis for symptom management even when experiencing adverse events related to concentration, memory or fatigue. Reducing use of prescription medication was a motivating factor for use of medical cannabis, and concerns regarding addiction, losing control or acting strangely were disincentives.

- However, a separate analysis concluded that the opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to very low-certainty evidence [66].

These results led an international guideline expert panel to issue a weak recommendation to offer a trial of non-inhaled medical cannabis or cannabinoids, in addition to standard care and management (if not sufficient) in people living with chronic cancer or noncancer pain (figure 1) [68].

Choosing an agent for a therapeutic trial

- **Dronabinol** – Until cannabinoid preparations become available and approved for pain the use of a cannabinoid for cancer pain must employ a drug that is marketed for purposes other than pain, specifically dronabinol (or nabilone, where available). If a therapeutic trial is offered, dronabinol usually is started at a dose of 2.5 mg once or twice daily and titrated. Nabilone should be started at 0.5 to 1 mg at night and titrated up to 3 mg twice daily, or higher if tolerated. Nabiximols oral spray should be initiated at no more than two sprays per day, evenly distributed over the course of the day. The use of smoked, vaporized, or ingested cannabis (marijuana) continues to be controversial.

- **Medicinal cannabis** – Medical use of smoked, vaporized, or ingested cannabis is legal in several countries, including the Netherlands and Canada. However, cannabis use is still illegal in the United States at the federal level (which considers marijuana a schedule I controlled substance) but is legal in most states. Clinicians may not prescribe cannabis but the states that have legalized medical use may rely on clinician assessment to determine eligibility for treatment and recommended formulation and dose [69]. There are no randomized studies of inhaled cannabis for cancer related pain, although an individual patient data meta-analysis of five, randomized, double-blind, placebo-controlled trials [53,54,70-72] of inhaled whole-leaf cannabis for chronic neuropathic noncancer-related pain (n = 178 patients) concluded that the OR for more than a 30 percent reduction in

subjective pain scores for inhaled cannabis versus placebo was 3.2 (95% credible interval [CRI] 1.59-7.24), and the number needed to treat to see benefit in one patient was 5.53 (95% CRI 3.35-13.7) [60].

Although severe or chronic pain accounts for over 90 percent of the qualifying conditions for use of medicinal cannabis among registered users in the states in which it is legal [73-76], its value for the treatment of chronic cancer pain remains uncertain. Some clinicians have embraced the approach, viewing the extant data and clinical anecdotes as sufficiently compelling to provide broad support. Other clinicians are hesitant, however. Given the heterogeneous legal status of marijuana, especially within the United States, the differences in cannabinoid concentrations across strains of cannabis and available products [77], the inability to stipulate, know, or titrate the dose taken by the patient, the general paucity of evidence-based information about efficacy and potential drug-drug interactions, and concerns about respiratory effects and cancer risk in cannabis smokers [55,78-83], clinicians may decide to recommend against its use, even in jurisdictions where it is legal. Given the state of the science and the sociopolitical complexities, each clinician must make his or her own decision while hopefully keeping an open mind. Should patients experience pain that is refractory to conventional therapies or report using and benefitting from cannabis, it is reasonable to accept a patient's decision to try medical cannabis and continue its use if it is helpful.

- **CBD oil** – CBD (cannabidiol) is a naturally occurring molecule without psychoactive properties. It can be procured by patients from legal marijuana dispensaries, online companies, or street suppliers (CBD oil [nutraceutical]). An approved formulation of CBD oil (pharmaceutical) is now available in the United States as a purified product available by prescription (Epidiolex) and approved for treatment of some types of refractory epilepsy in children. (See "Dravet syndrome: Management and prognosis" and "Lennox-Gastaut syndrome".)

  Although CBD oil (herbal) is used by patients as a nutraceutical for a variety of other conditions, there are few data on its benefits or risks in any type of cancer pain, and use cannot be recommended. A single phase II randomized double-blind placebo-controlled trial of CBD oil for relief of symptoms in advanced cancer concluded that CBD oil did not add value to the reduction in symptom distress (including pain) provided by specialist palliative care [84].

Adverse effects — The central nervous system effects of the cannabinoids and cannabis may provoke varied adverse effects, including drowsiness or somnolence, dizziness, fatigue, disorientation or confusion, mood change (eg, euphoria or dysphoria), loss of balance, and

hallucinations [58,85]. Dry mouth may occur and some patients develop nausea and vomiting, which may be severe in some patients. Cardiovascular effects, including postural syncope and arrhythmias are also reported, and myocardial infarction has occurred, although the frequency with which these effects occur is unknown [86]. The long-term adverse effects of medical cannabis use are largely unknown, but low-strength evidence suggests that smoking marijuana is associated with cough, sputum production, and wheezing [81]. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

Chronic use of cannabis also has been associated with withdrawal symptoms after sudden cessation of use. These symptoms, such as anxiety, headache, and hypersomnia, could potentially manifest after hospital admission. (See "Cannabis withdrawal: Epidemiology, clinical features, diagnosis, and treatment".)

Topical therapies — A trial of a transdermal lidocaine patch is reasonable in patients who have localized, peripherally generated pain. Other commercially-available topical treatments that may be beneficial in specific circumstances include local anesthetic formulations (eg, eutectic mixture of local anesthetics [EMLA] cream for the pain of a needle stick or an incision), capsaicin for neuropathy-related pain, nonsteroidal anti-inflammatory drugs (NSAIDs) for local or locoregional pain; other drugs, such as TCAs, have been compounded for topical use.

A variety of topical therapies have been used to treat diverse pain syndromes and may be considered a multipurpose analgesic approach. Topical therapies have the potential to deliver analgesic compounds directly to the site that is presumably responsible, at least in part, for the persistent pain. The relative lack of systemic toxicity offers a therapeutic advantage that may be particularly relevant to the medically ill. Although topical analgesics have been used mostly for neuropathic pain, they have the potential for broader application. An overview of topical analgesics for treatment of superficial painful conditions is provided in the table (table 4).

Local anesthetics — The most widely used topical therapies for pain contain local anesthetics. Lidocaine 5% patches may be applied to treat focal or regional pain of all types; lidocaine gels and creams are less often used because they have to be reapplied two to four times per day, but they are less expensive.

The evidence to support benefit from topical lidocaine is relatively weak, however. A 2014 systematic review concluded that there is little evidence to support the use of topical lidocaine to treat neuropathic pain, but results from individual studies and clinical experience suggest that it can be effective in some patients [87]. Surveys of studies using relatively high concentrations of topical lidocaine gel suggest that a compound of this type can produce benefits for focal, peripherally generated pain, such as occurs in postherpetic neuralgia [88].

(See "Postherpetic neuralgia", section on 'Topical therapy for patients with milder symptoms' and "Pharmacologic management of chronic non-cancer pain in adults", section on 'Topical agents'.)

Although the current approved use for the lidocaine patch (based on clinical trials) is a 12-hours-per-day dosing regimen, some patients find that pain relief does not last 24 hours, and continuous application is common in the clinical setting. Multiple patches are often used together. There are limited data that indicate a high level of safety with four patches applied for 24 hours a day for up to 72 hours [89].

The most frequently reported adverse event from the lidocaine patch is mild to moderate skin irritation at the patch application site, which seems to be related to the vehicle rather than to lidocaine. There is only a remote risk of toxicity from systemic absorption of lidocaine, but it may be a concern in patients with impaired renal or hepatic function [90,91]. Cost may be prohibitive.

Lidocaine also is available in combination products. One such product is a lidocaine-menthol patch. Menthol is thought to contribute to the analgesic efficacy of the patches by dilating the blood vessels and causing a sensation of coldness followed by an analgesic effect. All patches are recommended to be left in place for up to 12 hours, and no information is available on continuous application.

Another combination product is a mixture of prilocaine and lidocaine, which is known as EMLA cream. EMLA cream is capable of penetrating the skin and producing a dense, local, cutaneous anesthesia [92]. This product and other similar formulations have been approved to prevent the pain of needle puncture or incision. In cancer patients who are having an invasive procedure, such as a lumbar puncture, or having a subcutaneous port accessed with a needle, application of a thin layer under an occlusive dressing is usually very effective though relatively expensive.

Capsaicin — Capsaicin, a naturally occurring constituent of the chili pepper, depletes substance P from the terminals of afferent C fibers. Topical application of a commercially available capsaicin cream or low-dose transdermal patch (strength varying from 0.025 to 0.1 percent), which are available over the counter in the United States, has yielded weak to moderate analgesic effects in controlled trials focusing on patients with various types of neuropathic and/or joint pain (table 4); few of these trials included patients with cancer-related neuropathic pain [93-96]. Burning at the application site, which is often transitory, is the major side effect and may lead to treatment discontinuation. Application three to four times daily for a period of at least a week is needed to determine benefit.

Capsaicin also is available in a high-concentration patch (8 percent capsaicin, Qutenza), which requires a prescription, and is approved for treatment of postherpetic neuralgia and painful diabetic peripheral neuropathy in the United States and for all types of peripheral neuropathic pain in the European Union. Efficacy was addressed in a year 2017 Cochrane review of eight placebo-controlled trials (2488 participants; four trials of postherpetic neuralgia, two of painful human immunodeficiency virus-related neuropathy, one of diabetic neuropathy, and one of patients with persistent pain following inguinal herniorrhaphy; no patient had cancer-related pain); six of the eight trials used 0.04% topical capsaicin as an "active" placebo) [97]. The authors concluded that high-concentration capsaicin generated more patients with moderate or substantial levels of pain relief than use of a much lower concentration of capsaicin, but that the quality of the evidence was moderate to very low. Local adverse events were common but not consistently reported.

High-concentration capsaicin patches are typically administered as a single 60-minute application. However, a single application for 30 minutes may be efficacious for several months, and treatment can be repeated [98]. Treatment must be administered by a health care professional, and patients are monitored for up to two hours after treatment. Eye and mucous membrane exposure must be avoided. To manage local pain from capsaicin application, the skin is pretreated with a local anesthetic such as topical lidocaine.

Anti-inflammatory and antidepressant drugs — Numerous anti-inflammatory drugs have been investigated for topical use. A diclofenac patch and gel are commercially available in the United States; others are available outside of the United States (table 4).

A 2017 Cochrane review concluded that there is overall strong evidence that these compounds are effective for acute musculoskeletal pain and low-quality evidence that they can help with chronic musculoskeletal pain [99]. Although there are no data on effectiveness as an adjuvant for treatment of cancer-related or cancer-treatment-related pain, evidence of safety and efficacy is sufficient to warrant a therapeutic trial in patients with small areas of local or locoregional pain of any cause. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Topical agents'.)

Evidence for the analgesic efficacy of topical TCAs is conflicting [100,101], but a cream containing one of these drugs may be tried local or regional pain. Topical doxepin is commercially available for the short-term management of pruritus and it may be considered for an analgesic trial. (See "Pruritus: Therapies for localized pruritus".)

Other topical drugs — Other drugs have been used empirically in specially compounded creams for use in patients with pain. The most popular are ketamine and gabapentin, but a

variety of others are in use. At least one trial suggests potential benefit for a compounded topical gel containing baclofen, amitriptyline, and ketamine in patients with painful chemotherapy-induced peripheral neuropathy (CIPN) [102]. Supporting data overall are very meager or absent, however, a 2020 guideline from the American Society of Clinical Oncology on treatment for CIPN concluded that no recommendation may be made about the use of topical amitriptyline and ketamine with or without baclofen for this use [103]. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Topical treatments containing amitriptyline and ketamine with and without baclofen'.)

Botulinum toxin — Botulinum toxin type A injections have been used for treatment of refractory pain in migraine, trigeminal neuralgia, postherpetic neuralgia, and other focal pain syndromes. (See "Postherpetic neuralgia", section on 'Botulinum toxin' and "Chronic migraine", section on 'Second- and third-line agents' and "Trigeminal neuralgia", section on 'Alternatives and adjuncts to first-line therapy'.)

Emerging evidence suggests that botulinum toxin might also be effective for other types of otherwise refractory chronic pain [104], although the only data in cancer patients are in head and neck cancer patients with painful neck contracture after chemoradiation, paraneoplastic Raynaud phenomenon in a patient treated for lung cancer, and focal pain at the site of radiation or surgery [105-107].

PATIENTS WITH NEUROPATHIC PAIN

Neuropathic pain may be caused by the cancer (eg, radiculopathy from local tumor invasion), antineoplastic treatment (eg, chemotherapy-induced peripheral neuropathy [CIPN]), or by comorbidities such as diabetes. (See "Overview of cancer pain syndromes", section on 'Tumor-related neuropathic pain' and "Overview of cancer pain syndromes", section on 'Chemotherapy-related neuropathy'.)

Adjuvant analgesics are commonly considered for this indication and, with the sole exception of CIPN, best practices in the management of cancer-related neuropathic pain are generally extrapolated from guidelines developed for chronic noncancer conditions, such as diabetic painful neuropathy, postherpetic neuralgia, and others.

General principles

- **Timing and treatment selection** – As noted above, there are no published data that inform the decision about the timing of adding an adjuvant analgesic to the pain control regimen therapy in patients with cancer-related pain, including neuropathic pain, and this

remains a matter of clinical judgment. (See 'Integration into cancer pain management' above.)

As discussed in more detail below, the management of cancer survivors with neuropathic pain mirrors populations with chronic neuropathic pain unrelated to cancer. Trials of adjuvant analgesics are provided and opioid therapy is considered for those with refractory pain after a careful evaluation of potential benefits and risks.

In the setting of active cancer, some experts advocate a trial of an adjuvant analgesic for neuropathic pain only if the response to an opioid has been unsatisfactory, (ie, after an opioid has been titrated to optimize the balance between analgesia and side effects). Others advocate early use of adjuvant analgesics, either alone or in tandem with cautious opioid titration [108]. Evidence to guide the best approach is lacking. Although neuropathic pain may be relatively less responsive to opioids than other types of cancer-related pain, the outcome of an individual patient cannot be predicted and a favorable response to opioid-based analgesia is often possible. Given the acceptance of opioid therapy as the first line approach for moderate or severe pain related to active cancer, for most patients, we prefer to offer an opioid first and employ the adjuvant drugs to manage inadequate opioid responsiveness. (See "Assessment of cancer pain" and "Cancer pain management with opioids: Optimizing analgesia".)

The adjuvant analgesics usually selected for neuropathic pain include drugs categorized as multipurpose analgesics and drugs that are used selectively for neuropathic pain. A common approach first considers whether the extent of the pain permits use of a topical drug such as lidocaine at least initially. For systemic therapy, the usual first-line drug is one of the gabapentinoids (either gabapentin or pregabalin), unless the patient has a mood disorder that would be concurrently targeted by an analgesic antidepressant or the patient has a chemotherapy-induced painful neuropathy, in which the usual first-line systemic therapy is duloxetine.

- **Active cancer versus cancer survivors** – The foregoing recommendation to optimize an opioid regimen before considering treatment with an adjuvant analgesic refers to the population with active cancer [109]. Neuropathic pain also occurs in cancer survivors with no active disease (eg, those with post-treatment neuropathic pain, such as with a postmastectomy pain syndrome, oxaliplatin-related chronic painful neuropathy). In this large group of patients, long-term opioid therapy for chronic pain is perceived to have a more limited role, one that mirrors the role of opioid therapy in chronic noncancer pain syndromes. (See "Postmastectomy pain syndrome: Risk reduction and management",

section on 'Pharmacotherapy' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Specific interventions that are recommended'.)

Cancer survivors with chronic neuropathic pain typically receive trials of adjuvant analgesics, and opioids are only considered on a case-by-case basis, usually after other therapeutic trials have been ineffective. This more limited role reflects concern about the ongoing risks associated with opioid drugs and the need for careful long-term management of adverse effects related to both drug toxicities and abuse liability. (See "Prevention and management of side effects in patients receiving opioids for chronic pain" and "Cancer pain management: General principles and risk management for patients receiving opioids".)

A high degree of caution in the use of long-term opioid therapy is also warranted in some populations with limited or indolently growing neoplasms, whose pain syndromes may mirror those experienced by cancer survivors without active disease. A careful assessment of risk and benefit should always be performed, and a commitment to long-term opioid therapy should be justified by a favorable response and responsible drug-taking behavior.

Our suggested approach — The following represents our general approach to these patients:

- Cancer-related neuropathic pain syndromes vary. Those associated with focal, local, or regional pain that may be amenable to a topical treatment (eg, focal chest pain due to painful intercostal mononeuropathy related to invasion of the chest wall by lung cancer) should be considered for a trial of topical lidocaine usually in combination with systemic analgesic therapy. In the context of active cancer, systemic analgesia usually involves a trial of an opioid and an orally-administered adjuvant analgesic is added if the opioid does not provide a favorable balance between analgesia and side effects. If the neuropathic pain is a post-treatment syndrome in a cancer survivor, systemic trials of adjuvant analgesics are the preferred starting point for systemic therapy and the addition of an opioid is considered on a case-by-case basis. (See 'General principles' above.)

- If the pain syndrome is CIPN, duloxetine is a preferred first-line agent because of the statistically significant (albeit clinically modest) reduction in pain associated with this agent in CIPN. Specific recommendations are provided elsewhere. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy".)

- For all other neuropathic pain syndromes, we suggest one of the gabapentinoids, either gabapentin or pregabalin, rather than an analgesic antidepressant. Pregabalin may be preferred because dose titration is simpler. (See 'Gabapentin and pregabalin' below.)

- However, if the neuropathic pain is associated with a depressed mood, we suggest an analgesic antidepressant rather than a gabapentinoid. For most patients we prefer a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine. (See 'Antidepressants' below.)

- The patient with advanced cancer and short prognosis also may be considered for a trial of a glucocorticoid (eg, dexamethasone 0.75 to 1.5 mg once or twice daily) particularly if pain is accompanied by other symptoms such as nausea.

- Patients who don't respond to the initial drug trial may be considered for trials of the alternative gabapentinoid or alternative analgesic antidepressants. Some experts follow an ineffective trial of a drug by choosing the next drug from a different class (eg, trying a gabapentinoid if an antidepressant is not effective), but there is no evidence to support this practice. Another option is to combine a gabapentinoid with a low-dose antidepressant (eg, desipramine). Clinicians should avoid prescribing combinations of antidepressants as this can induce the serotonin syndrome. (See "Serotonin syndrome (serotonin toxicity)".)

- If therapeutic trials of the gabapentinoids and the analgesic antidepressants prove unsatisfactory, sequential trials of other adjuvant drugs can be tried, although there is very little evidence to guide treatment selection and recommendations reflect a limited literature and clinical experience. The preferred alternatives are the anticonvulsants, oxcarbazepine or lacosamide, or the alpha-2 adrenergic agonist, tizanidine. A brief intravenous infusion of lidocaine, typically 2 to 4 mg/kg infused over 20 to 30 minutes in a monitored setting, has been used for severe neuropathic pain and can result in prompt pain reduction so that other strategies can be implemented more gradually. (See 'Sodium channel blockers' below.)

- A trial of non-inhaled medical cannabis or cannabinoids can be offered to patients with advanced cancer and neuropathic pain that has not adequately responded to opioids or other alternative adjuvant analgesics. (See 'Cannabis and cannabinoids' above.)

- For patients with refractory focal pain, botulinum toxin injection is another option. (See 'Botulinum toxin' above.)

- Treatment-refractory neuropathic pain may respond to ketamine, although the available evidence is limited. (See 'Ketamine and other NMDA receptor antagonists' below.)

Individual treatments

Antidepressants — As noted above, the most useful analgesic antidepressants are the SNRIs (with duloxetine having the most robust evidence, at least for CIPN) and the secondary amine tricyclic antidepressant (TCA) compounds (eg, desipramine). Evidence of analgesic efficacy for a variety of types of chronic pain has been demonstrated in randomized controlled trials and meta-analyses. (See 'Selection of agent and dose' above.)

Positive results with duloxetine in a single, randomized, double-blind, placebo-controlled crossover trial conducted in patients with painful CIPN after treatment with taxane- or platinum-containing chemotherapy support the view that in this setting, duloxetine is an appropriate first-line agent, particularly in view of a negative gabapentin trial in this setting [37] and no other randomized trials showing benefit for any other strategies for CIPN, painful or not. However, additional data will be needed to establish the superiority of duloxetine or any other antidepressant over the gabapentinoids in these patients and to establish the efficacy of duloxetine in patients with CIPN from other drugs, such as vinca alkaloids. Specific recommendations in this setting are provided elsewhere. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Gabapentinoids'.)

Most experts also consider the analgesic antidepressants to be preferred first-line treatments for neuropathic pain that is associated with a significant depressed mood, notwithstanding the lack of trials comparing antidepressants with other strategies (such as anticonvulsants) in this setting. For most patients, an SNRI such as duloxetine is preferred over other antidepressants such as a TCA. (See 'Analgesic antidepressants' above.)

For nondepressed patients with neuropathic pain who achieve meaningful, but insufficient analgesia with a gabapentinoid, an analgesic antidepressant may be added (eg, low-dose desipramine) may be added if the risks are acceptable.

It is important to emphasize that these conclusions are not evidence-based and that additional trials are needed. In particular, few data have directly compared antidepressants versus anticonvulsants in any group of patients with cancer-related neuropathic pain, precluding robust evidence-based recommendations:

- A systematic review of the effectiveness of antiseizure medications or antidepressants added to opioids for neuropathic pain from cancer, described above, concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain; benefit was strongest for gabapentin and was counterbalanced by an increase in adverse events [110]. (See 'Gabapentin and pregabalin' below.)

- A second systematic literature review concluded that the absolute benefit for all adjuvant analgesics, including antidepressants, greatly outweighed the absolute risk for harm, but that all studies had low methodologic quality, precluding any conclusions about the relative effect sizes of antidepressants relative to any other medication groups, including gabapentinoids [111].

Anticonvulsants — The anticonvulsants represent a diverse group of drugs that vary in mechanisms and clinical effects (table 1 and table 2). Two of the drugs in this group (the gabapentinoids gabapentin and pregabalin) are approved in the United States for treatment of various painful conditions and are considered the first-line approach for patients without comorbid depression who have neuropathic cancer pain other than painful neuropathy due to chemotherapy (an evidence-based approach for taxane or platinum-based chemotherapy-induced painful neuropathy). (See 'Antidepressants' above.)

Gabapentin and pregabalin

- **Mechanism of action** – The gabapentinoids act by binding to the alpha-2-delta protein modulator of the N-type voltage-gated calcium channel. Binding to this protein reduces calcium influx into the neuron and lessens the likelihood of depolarization.

- **Side effects and precautions** – Unlike all other anticonvulsants, gabapentin and pregabalin are not metabolized in the liver, and they have few drug-drug interactions, with the important exception of enhancing the central nervous system (CNS) depressive effects of other centrally-acting drugs. This includes the opioids, and there is an increased risk of oversedation or a serious adverse consequence (including death) when gabapentin or pregabalin is added to an opioid regimen [112,113]. The risk is highest in cancer patients with multiple comorbidities who are taking multiple centrally-acting drugs, and it must be recognized and carefully monitored.

  Given this potential for CNS depression, gabapentinoids should be administered cautiously to patients who are receiving centrally-acting drugs with sedative effects, especially opioid drugs. In 2020, the US Food and Drug Administration (FDA) mandated revisions to the labeling regarding the risk of severe and life-threatening respiratory depression with use of gabapentinoids, particularly in combination with CNS depressants (eg, opioids), in those with underlying respiratory disease and in older adults [114]. (See "Prevention and management of side effects in patients receiving opioids for chronic pain", section on 'Somnolence and mental clouding'.)

  Both of the gabapentinoids are excreted by the kidneys, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness,

and somnolence; edema and weight gain are less common.

- **Efficacy** – Gabapentin and pregabalin have been extensively studied for diverse types of neuropathic pain, particularly postherpetic neuralgia and painful diabetic neuropathy. (See "Postherpetic neuralgia", section on 'Gabapentinoids for most patients with moderate or severe pain' and "Management of diabetic neuropathy", section on 'Pain management'.)

  Efficacy is also suggested for patients with neuropathic pain related to cancer or its treatment, although fewer data are available:

  - In three, small, randomized, placebo-controlled trials involving populations of opioid-treated patients with cancer-related neuropathic pain, the addition of gabapentin or pregabalin was significantly better than placebo at improving neuropathic pain and dysesthesias [115-117]; one of these trials directly compared gabapentin with pregabalin and is discussed in more detail below [116].

    Another placebo-controlled randomized trial of gabapentin for painful CIPN failed to show any benefit for gabapentin. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Gabapentinoids'.)

  - A benefit for pregabalin alone (ie, without opioids) in the treatment of radiation therapy-related neuropathic pain was also suggested in a randomized, placebo-controlled, double-blind trial of 128 head and neck cancer survivors [118]. Patients treated with dose-adjusted pregabalin (16 weeks of treatment, starting at 75 mg daily and increasing up to 300 mg twice daily depending on pain relief and tolerability) had a significant reduction in their mean pain intensity (pain intensity reduction 2.44 versus 1.58 on an 11-point numeric rating scale, adjusted mean difference 0.87, 95% CI 0.03-1.44). Patients receiving pregabalin also had better mood states and a higher quality of life, and fewer required rescue pain medication (13 versus 41 percent) during the study period.

  - A systematic review of the effectiveness of antiseizure medications or antidepressants added to opioids for neuropathic pain from cancer concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain; the effect was strongest for gabapentin but was counterbalanced by an increase in adverse events [110].

    By contrast, a second systematic literature review of the evidence for pharmacologic treatment of neuropathic cancer pain concluded that the absolute benefit for all agents (antidepressants, anticonvulsants) greatly outweighed the absolute risk for harm, but

that all studies had low methodologic quality, precluding conclusions about the relative effect sizes of the different medication groups [111].

- **Choice of agent and dose** — If available, and not prohibitively expensive for the patient, pregabalin may be preferred for an initial trial of a gabapentinoid because dose adjustments are simpler than they are for gabapentin.

  A typical starting dose of pregabalin is 50 to 75 mg twice daily. Further escalation to the usual effective dose of 150 to 300 mg twice daily typically is accomplished in two to three steps over one to two weeks. In medically frail cancer patients and those with significantly impaired kidney function, the starting dose should be reduced to 25 mg per day, and titration is slower.

  Gabapentin is often initiated at a dose of 300 mg per day (or 100 mg per day in the medically frail or renally impaired). The dose is doubled and administered as two divided doses per day after a few days. The dose is then gradually escalated every few days while monitoring analgesia and side effects. If pain relief does not occur, in the absence of an analgesic ceiling (dose escalation does not yield more analgesia) and adverse effects, escalation can extend to 3600 mg per day, administered in two to three divided doses. Occasional patients benefit from even higher doses. If possible, it is preferable to taper these drugs prior to discontinuation.

  There are important pharmacokinetic differences between gabapentin and pregabalin that may impact choice of treatment:

  - Absorption and entry of gabapentin into the CNS is facilitated by a saturable transporter in the small bowel and CNS. At relatively higher doses (approximately 1800 mg per day, but could be higher or lower in individual cases (table 2)), the kinetics become nonlinear and there is less complete absorption with each dose increment. These saturable kinetics mean that gabapentin has a pharmacokinetic "ceiling," which coexists with a possible pharmacodynamic "ceiling" of the type that is observed with all adjuvant analgesics (ie, at some point, a maximum effect is reached and further dose increments provide no additional benefit).

  - By contrast, absorption of pregabalin is not dependent on a saturable transport mechanism, and this drug only has the unpredictable pharmacodynamic ceiling. This linear pharmacokinetic profile simplifies dosing of pregabalin compared with gabapentin.

From an efficacy standpoint, studies suggest that individual patients may be responders to gabapentin, pregabalin, both, or neither [119]. The superiority of one drug over the other was directly tested in a double-blind trial that randomly assigned 120 patients with cancer and severe neuropathic pain to gabapentin (900 mg daily for one week, followed by 1200 mg daily for one week, then 1800 mg daily), pregabalin (150 mg daily for one week, followed by 300 mg daily for one week, then 600 mg daily), amitriptyline (50 mg daily for one week, followed by 75 mg per day for one week, then 100 mg daily at bedtime), or placebo [116]. The primary outcome measure was the global intensity of pain as measured on a 100 mm Visual Analog Scale (VAS). By week 4, the mean VAS score with pregabalin was significantly less than that with gabapentin, and the percentage of patients requiring rescue morphine in the placebo, amitriptyline, gabapentin, and pregabalin groups was significantly different (100, 57, 33, and 17 percent, respectively).

While this study suggests that pregabalin may have superior efficacy, study limitations (ie, unclear methods for randomization, blinding or statistical analysis, and the primary endpoint analysis was not conducted in an "intention to treat" population) preclude definitive conclusions. In addition, the drugs were tested at doses that may not be fairly compared; the initial dose of pregabalin was relatively high, while the top dose of gabapentin would not be considered relatively high for this drug. For all of these reasons, it cannot be concluded that pregabalin is superior to gabapentin for treatment of neuropathic pain.

Other anticonvulsants — The non-gabapentinoid anticonvulsants have diverse mechanisms and data pertaining to analgesic efficacy for neuropathic pain are limited. A small number of these drugs (oxcarbazepine, lacosamide) may be considered for a trial in patients who have not responded satisfactorily to the gabapentinoids and other preferred agents, such as the antidepressants [120].

Older anticonvulsants, such as carbamazepine, valproate, and phenytoin, are perceived as having potential analgesic effects based on trials performed, in some cases, many decades ago. Systematic reviews have concluded that the evidence for any of these drugs in neuropathic pain is low quality [110,111,121,122]. The newer anticonvulsants have a better adverse effect profile, but again, have very limited evidence of efficacy.

- Oxcarbazepine – Oxcarbazepine is a metabolite of carbamazepine that has similar anticonvulsant properties and a safer pharmacologic profile. Although the quality of the evidence is limited [123], it has been shown to be analgesic in trigeminal neuralgia and several other types of peripheral neuropathic pain [124]. A trial of this drug may be

considered after trials of the gabapentinoids and perhaps one or two of the analgesic antidepressants have proven unhelpful.

- Lacosamide – Lacosamide, a relatively new anticonvulsant, is a sodium channel modulator with a unique mechanism of action. A Cochrane review concluded that lacosamide has limited efficacy in treatment of painful diabetic neuropathy [125]; there are no data in patients with cancer-related pain. Based on these limited efficacy data, this agent also could be considered among those that are potentially useful for treatment of refractory neuropathic pain.

- Lamotrigine – Lamotrigine has been effective in studies of central pain, trigeminal neuralgia, painful human immunodeficiency virus polyneuropathy, and postherpetic neuralgia, but it has not been analgesic in other trials, including one conducted in patients with painful CIPN [126]. This drug is associated with a small risk of severe cutaneous hypersensitivity, which is relatively higher in younger patients. It should not be used in patients under the age of 15, and slow titration of the dose from a low initial dose is necessary to reduce the risk of hypersensitivity. Given the limited evidence of efficacy, the need for slow titration, and the risk of severe cutaneous hypersensitivity, this drug is not a preferred second-line agent for neuropathic pain and usually is considered only after neuropathic pain has proved to be refractory to other preferred drugs.

- Topiramate – Topiramate, an effective drug for prevention of episodic migraine, has been variably effective in studies of neuropathic pain. Although anecdotal experience suggests that some patients with cancer and neuropathic pain derive benefit, it is generally considered only after other second-line drugs have been proved ineffective [127,128]. (See "Preventive treatment of episodic migraine in adults", section on 'Topiramate'.)

- **Others** – As noted, the data supporting the analgesic efficacy of valproate and phenytoin are limited [129,130]. Although these drugs may be considered for trials in patients with intractable neuropathic pain, conventional practice in countries that have access to newer agents relegates them to trials after other anticonvulsants have been demonstrated to be ineffective.

  There is no evidence to support the analgesic efficacy of levetiracetam, zonisamide, and tiagabine, and in the absence of additional data, these drugs usually are not considered unless others are not available.

  Clonazepam is a benzodiazepine. Very meager data support analgesic efficacy in patients with neuropathic pain [131]. Its anxiolytic effects may be favorable, however, and a trial is

sometimes considered in the patient with refractory neuropathic pain associated with anxiety.

Other drugs — Patients who do not respond favorably to trials of the gabapentinoids and analgesic antidepressants may be considered for trials of other drugs categorized as multipurpose adjuvant analgesics. A trial of an alpha-2 agonist, such as tizanidine, or a trial of a cannabinoid, such as dronabinol, might be considered. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above.)

Topical agents (starting with local anesthetic formulations such as a lidocaine patch) should always be considered for an early trial when neuropathic pain is focal or regional [132]. (See 'Topical therapies' above and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Topical treatments containing amitriptyline and ketamine with and without baclofen'.)

Other drug classes play a far less prominent role in the clinical strategy for cancer-related neuropathic pain. Patients with advanced illness and a short prognosis could be considered for a trial of a low-dose glucocorticoid (see 'Glucocorticoids' above). Occasional patients with refractory neuropathic pain who have not responded to other drugs may be considered for trials of one or more of these uncommon treatments based on very limited data and anecdotal experience.

Sodium channel blockers — Blockade of sodium channels has been recognized as an analgesic mechanism for decades, and the potential role of the new sodium channel modulator lacosamide was mentioned above. (See 'Other anticonvulsants' above.)

Treatment approaches using older sodium channel blockers include oral therapy with antiarrhythmic drugs, such as mexiletine or tocainide, or parenteral therapy, usually with lidocaine. The analgesic effects and generally favorable safety profile of these drugs are strongly supported by the literature [133,134]; the usual side effects are dizziness, nausea, and fatigue.

The use of a brief intravenous infusion of lidocaine, typically 2 to 4 mg/kg infused over 20 to 30 minutes in a monitored setting, can be beneficial in the context of very severe neuropathic because of its potential for rapid onset relief. If available, it can be used in the hope of gaining time so that other strategies can be implemented more gradually.

Ketamine and other NMDA receptor antagonists — Ketamine is used by specialists in palliative medicine to address refractory pain at the end of life [135,136]. Anecdotally,

treatment-refractory pain, usually neuropathic, earlier in the course of illness also is considered a potential indication for ketamine, although the available evidence is limited.

- Ketamine

  - **Mechanism of action** – The N-methyl-D-aspartate (NMDA) receptor is involved in both the sensitization of central neurons and the functioning of the opioid receptor, and there is evidence that one of the commercially available NMDA receptor antagonists, ketamine, has analgesic properties [137].

  - **Efficacy** – Many experts believe that ketamine at subanesthetic doses may be useful as a brief infusion for treatment of severe pain [135,136], or as a more prolonged infusion or oral therapy in the context of refractory pain associated with advanced illness [138]. The evidence to support benefit of ketamine as an adjuvant to opioid therapy is quite limited, however [139-145]. A 2017 Cochrane review of three of these trials (the rest were excluded because of methodologic problems or an extremely small number of patients completing the study) [139,141,144] concluded that the evidence was insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain [146].

    Nevertheless, use of parenteral ketamine for chronic pain is supported in consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists [147], and ketamine continues to be used by specialists in palliative medicine to address refractory pain at the end of life [135,136]. Anecdotally, treatment-refractory pain, usually neuropathic, earlier in the course of illness also is considered a potential indication.

  - **Side effects and precautions** – The side effect profile of ketamine, particularly psychotomimetic effects (including symptoms of dissociation, hallucinations, and delirium), can be problematic [148-150], and as a result, the most common use is for short-term therapy in a monitored setting. Based upon anecdotal observations that treatment with a benzodiazepine, such as lorazepam, or a neuroleptic, such as haloperidol [151], reduces the risk of psychotomimetic effects from ketamine, most practitioners co-administer one of these drugs prior to the start of the infusion and repeatedly during longer-term treatment. Gradual dose titration of ketamine may also reduce the incidence of psychotomimetic effects [152].

  - **Route of delivery and dose** – Ketamine may be delivered by subcutaneous or intravenous continuous infusion, brief infusion, or repeated bolus, or by the oral route:

- Brief infusion (eg, 100 mg per day, escalating by 100 mg per day increments, for two to five days) has been termed "burst" therapy, and may be used to manage episodes of severe pain [135,153]. However, this approach should be used cautiously given the risk of adverse effects with rapid dose escalation.

- Continuous infusion protocols may start with a loading bolus (eg, 0.1 to 0.5 mg/kg), followed by 0.05 to 0.2 mg/kg per hour [148,154]. The rate can be increased every few hours if pain relief is inadequate and side effects are tolerable. An alternative approach starts with 50 to 100 mg per day, irrespective of weight, with a daily dose increase by 25 to 50 percent, depending on effects.

- Oral ketamine can be started at 10 to 25 mg three or four times daily and then up-titrated until benefit or side effects emerge. In one retrospective survey, the mean effective total daily oral dose was 2 mg/kg [155].

- **Others** – Other NMDA receptor antagonists, such as memantine, amantadine, and dextromethorphan, have been studied in neuropathic pain states, with mixed results [156]. They are rarely considered for trials in cancer-related neuropathic pain that has not responded to other agents.

GABA receptor modulators — Gamma-aminobutyric acid (GABA) receptor modulators include the benzodiazepines, which bind to the $GABA_A$ receptor subtype, and baclofen, which binds to the $GABA_B$ receptor subtype.

Benzodiazepines potentiate inhibitory effects of endogenous presynaptic GABA. As noted previously, the only benzodiazepine that is used for neuropathic pain is clonazepam, and this use is based on anecdotal observations. (See 'Other anticonvulsants' above.)

Baclofen reduces the release of excitatory neurotransmitters by binding to the $GABA_B$ presynaptic receptors within the brain stem, dorsal horn of the spinal cord, and other CNS sites. Baclofen is effective for the treatment of spasticity and also has established efficacy in trigeminal neuralgia. It has been used anecdotally for neuropathic pain of other types, including cancer pain [157]. A low starting dose of 5 mg twice daily can be gradually escalated to doses that may exceed 200 mg per day in some patients. (See "Trigeminal neuralgia", section on 'Alternatives and adjuncts to first-line therapy'.)

Recommendations of expert groups — Our recommendation for management of neuropathic pain in cancer patients are consistent with those of expert groups:

- Year 2007 recommendations for treatment of neuropathic pain (including that related to cancer or secondary to chemotherapy) are available from the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP) [108]. A stepwise approach to assessment and treatment is recommended in the IASP guidelines and is relevant to neuropathic cancer pain:
    - Assess the pain and establish the likely neuropathic etiology. The assessment should include identification of relevant comorbidities that may be impacted by treatment of neuropathic pain or require modifications in the initial treatment regimen. (See "Assessment of cancer pain".)
    - Initiate antineoplastic therapy for the disease causing the neuropathy, if applicable.
    - Initiate symptom treatment for the painful neuropathy. Recommended first-line treatments include certain antidepressants (ie, TCAs and SNRIs), gabapentinoids, and topical lidocaine. Opioid analgesics and tramadol are recommended generally as second-line treatments that can be considered for first-line use in select clinical circumstances.
- Guidelines from the National Comprehensive Cancer Network [158] and the European Association for Palliative Care [159] broadly concur with the IASP guidelines, suggesting that antidepressants or anticonvulsants are the preferred first-line coanalgesics for treatment of cancer-related neuropathic pain, either alone, or in combination with opioids in patients whose pain is only partially responsive to opioids.
- Updated 2020 guidelines from the American Society of Clinical Oncology suggest duloxetine for initial treatment of painful CIPN [103]. They did not limit this recommendation to taxane and platinum-related neuropathy. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine'.)

PATIENTS WITH BONE PAIN

Bone is the most common pain-sensitive structure affected by cancer. The assessment of a patient with new bone pain may suggest the presence of a primary bone tumor or bone metastases, for which local treatments such as radiation therapy, kyphoplasty, or surgery, may be needed. (See "Assessment of cancer pain" and "Epidemiology, clinical presentation, and diagnosis of bone metastasis in adults" and "Radiation therapy for the management of painful bone metastases" and "Clinical presentation and evaluation of complete and impending

pathologic fractures in patients with metastatic bone disease, multiple myeloma, and lymphoma" and "Assessment of cancer pain", section on 'Etiology'.)

The majority of patients with cancer-related bone pain require analgesia, and they are usually managed with a combined approach, utilizing nonsteroidal anti-inflammatory drugs (NSAIDs), unless they have a specific contraindication to use of these agents, plus an opioid, with or without an adjuvant analgesic used specifically for bone pain. (See "Cancer pain management: Use of acetaminophen and nonsteroidal anti-inflammatory drugs", section on 'Indications and contraindications'.)

Adjuvant analgesics to consider in this setting include osteoclast inhibitors (bisphosphonates, denosumab) and bone-seeking radiopharmaceuticals (table 1), glucocorticoids are usually reserved for patients with advanced illness and limited prognosis. (See 'Indications' above.)

The following represents our general approach to these patients:

- Osteoclast inhibitors are indicated, in conjunction with an opioid, for patients with symptomatic bone metastases from a variety of cancers. These drugs prevent skeletal-related events, improve quality of life, and can improve bone pain, although their analgesic effects are only modest. (See 'Osteoclast inhibitors' below.)

- Use of bone-targeted radiopharmaceuticals, such as radium-223, is typically reserved for the patient with multifocal bone pain that is refractory to other treatment. The majority of the data on efficacy are in patients with metastatic prostate cancer. (See 'Bone-targeted radiopharmaceuticals' below.)

- Glucocorticoids may be useful in patients with opioid-refractory bone pain. As noted, some experts try a low-dose regimen to address pain and concurrent symptoms (eg, fatigue, nausea, and dysphoria) when the cancer is advanced and prognosis is limited. These drugs also may be considered for short-term treatment, especially in patients with a "pain crisis," which is defined as severe and escalating pain that is not responding sufficiently to an opioid. (See 'Choice of agent and dose' above.)

Osteoclast inhibitors — For patients with metastatic bone disease, bisphosphonates and denosumab prevent skeletal-related events, including fracture, and they may also improve pain and quality of life. Bisphosphonates act by directly inhibiting osteoclast activity, stimulating osteoblasts to produce osteoclast-inhibiting factor, and causing osteoclast apoptosis. Osteoclast inhibition can also be achieved by targeting the receptor activator of nuclear factor kappa B ligand, a key component in the pathway for osteoclast formation and activation. (See

"Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors", section on 'Efficacy and dosing considerations for individual agents'.)

As adjuvant agents, there is evidence to support the analgesic potential of all osteoclast inhibitors, although benefit seems modest, particularly in the setting of metastatic non-small cell lung cancer (NSCLC) (see "Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors", section on 'Impact on quality of life'):

- In a Cochrane review, a significant improvement in bone pain was reported after receiving a bisphosphonate in patients with bone metastases from breast cancer in 6 of 11 studies [160].
- In at least one trial, intravenous ibandronate was as efficacious as a single fraction of radiation therapy for treatment of localized bone pain from metastatic disease in males with prostate cancer [161].
- On the other hand, a systematic review of bone-targeted agents in NSCLC concluded that the evidence for an analgesic effect of bisphosphonates or denosumab in patients with bone metastases was very weak [162].

Several reports note a modest but significant advantage for denosumab over zoledronic acid in terms of analgesic effect:

- One randomized trial comparing zoledronic acid with denosumab in 2046 patients with bone metastases from breast cancer specifically reported endpoints related to bone pain and quality of life [163,164]. Compared with zoledronic acid, fewer patients receiving denosumab who had no or mild pain at baseline progressed to moderate or severe pain (although the absolute difference was only 5 percent), there was an almost-four-month-longer delay in the median time to pain worsening to moderate or severe, and fewer shifted from no or low analgesic use to strong analgesic use. At the majority of time points, fewer denosumab-treated patients experienced a meaningful worsening of pain severity (≥2 point increase from baseline), although the difference was modest (absolute difference 3 percent) [163]. In addition, 10 percent more denosumab-treated patients had a clinically meaningful improvement in health-related quality of life relative to zoledronic-acid-treated patients, regardless of baseline pain levels [164]. (See "Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors", section on 'Efficacy'.)
- Other data are available from an integrated analysis of pain outcomes [165] with denosumab versus zoledronic acid derived from the original report of the above

mentioned trial [166] and two other phase III trials in patients with bone metastases from castration-resistant prostate cancer or other solid tumors, excluding multiple myeloma [167,168]. Treatment with either drug was associated with improvements in pain outcomes. Denosumab significantly delayed the time to increase in pain interference overall (11.1 versus 9.3 months) and the time to pain interference with activity (8.3 versus 7.4 months, hazard ratio 0.9, p = 0.009). Furthermore, fewer patients receiving denosumab shifted to using a strong opioid (as compared with no analgesic, a nonopioid analgesic, or a weak opioid; 7.7 versus 9.1 percent). Additionally, treatment with denosumab compared with zoledronic acid reduced the risk of and delayed the time to development of moderate or severe pain in patients both with (5.7 versus 3.9 months) and without a prior skeletal-related event (6.7 versus 4.8 months).

The choice of one agent over another for patients with bone metastases is based on many factors, including cost (which is higher for denosumab). However, one advantage of denosumab over zoledronic acid is that it is a quick monthly subcutaneous injection and not a prolonged intravenous infusion. On the other hand, for many patients the dosing interval for zoledronic acid can be extended to every three months rather than monthly, increasing convenience and decreasing cost. These issues are all addressed in detail elsewhere. (See "Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors", section on 'Efficacy and dosing considerations for individual agents'.)

Although generally well tolerated, bisphosphonates are associated with some potentially serious side effects, including impaired renal function, hypocalcemia, osteonecrosis of the jaw, an increased risk of atypical femur fractures during prolonged therapy, and severe (and occasionally debilitating) bone, joint, and/or muscle pain. Some of the same side effects are shared by denosumab (ie, osteonecrosis of the jaw, hypocalcemia and other electrolyte abnormalities), although impairment of renal function has not been seen. (See "Risks of therapy with bone antiresorptive agents in patients with advanced malignancy".)

Regardless of the agent chosen, given the modest analgesic effects of osteoclast inhibitors, in general, they should not be used alone for management of pain from bone metastases [169]. (See "Overview of therapeutic approaches for adult patients with bone metastasis from solid tumors", section on 'General approach to the patient'.)

Bone-targeted radiopharmaceuticals — Alpha- and beta-emitting radiopharmaceuticals (radium-223, strontium-89, and samarium-153) link a short-lived radiation source to a bone-seeking molecule. Once injected, the drug is taken up at the site of bone metastases and delivers radiation locally. Myelosuppression, which has been a particular concern with strontium-89, is less of a concern with radium-223, an alpha emitter.

Bone-targeted radiopharmaceuticals represent a useful treatment for multifocal bone pain, but treatment requires special skills and facilities. These agents have been used most often for males with metastatic prostate cancer; their use is discussed in more detail elsewhere. (See "Bone metastases in advanced prostate cancer: Management", section on 'Bone-targeted radioisotopes'.)

Glucocorticoids — The benefit of glucocorticoids as multipurpose analgesics is discussed above. (See 'Glucocorticoids' above.)

A short course of glucocorticoids (eg, oral dexamethasone 8 mg once daily from days 1 to 5) may also be useful to prevent the bone flare during radiation therapy for treatment of painful bone metastases [170], although concerns over side effects such as insomnia and hyperglycemia have tempered enthusiasm for this approach This subject is addressed in detail separately. (See "Radiation therapy for the management of painful bone metastases", section on 'Time course of relief and incidence of pain flare'.)

PATIENTS WITH MALIGNANT BOWEL OBSTRUCTION

Bowel obstruction is a well-recognized complication in patients with advanced intra-abdominal or pelvic tumors. Most of these patients are inoperable, and their survival is generally short. Some cases may be amenable to placement of a self-expanding metal stent. (See "Enteral stents for the management of malignant colorectal obstruction".)

For patients with inoperable intestinal obstruction who are not appropriate for a stent, decompression of gastric contents can also be achieved through placement of a percutaneous gastrostomy tube. However, these procedures provide only incomplete relief of distressing symptoms, and the ongoing presence of these tubes can be uncomfortable and distressing for the patient and his or her caregivers. (See "Palliative care of bowel obstruction in cancer patients", section on 'Patients who are not surgical candidates'.)

More recently, medical management of inoperable patients has focused on adequate control of pain, distention, and vomiting using hydration, opioids, and adjuvant medications that may reduce symptoms by lessening peritumoral edema (glucocorticoids) and diminishing intraluminal secretions and peristaltic movements (anticholinergic agents and octreotide). The use of these agents as adjuvant analgesics in this situation is discussed in detail elsewhere. (See "Palliative care of bowel obstruction in cancer patients", section on 'Pharmacologic management'.)

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: Neuropathic pain" 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)")

SUMMARY AND RECOMMENDATIONS

- **General concepts**
  - Adjuvant analgesics (coanalgesics) are drugs that have a clinical use other than pain but are used as analgesics in selected circumstances particularly when a patient is poorly responsive to opioids. The available agents are categorized on the basis of how they are used in clinical practice (table 1). (See 'Available agents and dose ranges' above.)
  - There are no published data that inform the decision about the timing of adjuvant analgesic therapy in patients with cancer-related pain. In contrast to patients with active cancer, in whom adjuvant analgesics may be added to the regimen for chronic pain that is poorly responsive to opioids, cancer survivors with chronic (typically neuropathic) pain usually receive an initial trial of an adjuvant analgesics, and opioids

are only considered on a case-by-case basis, for refractory pain. This more limited role reflects concern about the ongoing risks associated with opioid drugs and the need for careful long-term management of adverse effects related to both drug toxicities and abuse. (See 'Integration into cancer pain management' above.)

- **Chronic pain that is not predominantly neuropathic, or related to bone metastases or malignant bowel obstruction**

  - **Patients with focal peripherally generated pain** – A trial of topical therapy, beginning with a transdermal lidocaine patch, can be offered to patients who have focal, peripherally generated pain. (See 'Topical therapies' above.)

  - **Patients with more generalized pain** – In the setting of active cancer, a patient with chronic cancer pain that is not predominantly neuropathic or related to bone metastases or bowel obstruction should be considered for a trial of an analgesic antidepressant. Particularly for the patient who also has a depressed mood, we suggest an early trial of an analgesic antidepressant rather than a different adjuvant analgesic (**Grade 2C**). For most patients, we prefer duloxetine. If duloxetine is unavailable or poorly tolerated, our preferred alternative analgesic antidepressants include a different serotonin-norepinephrine reuptake inhibitor (SNRI) or a secondary tricyclic drug, such as desipramine. A trial of bupropion is reasonable if cancer pain is complicated by fatigue or somnolence, but the drug should be avoided in patients at risk for seizures. (See 'Analgesic antidepressants' above.)

  - **Other options** – Other options are alternatives for patients without depressed mood or second-line options that can be tried based on comorbidities and patient preference:

    - Glucocorticoids can be useful in the treatment of a variety of types of cancer pain. Because of this potential for toxicity, a careful risk-to-benefit analysis is warranted whenever a glucocorticoid is being considered for pain management, which considers the availability of other treatments, the planned duration of treatment, other symptoms, treatment context, and life expectancy. (See 'Glucocorticoids' above.)

    - A trial of non-inhaled medical cannabis or cannabinoids can be offered to patients with advanced cancer and refractory pain. Patients who place a relatively high value on small or very small improvements in self-reported pain intensity, physical functioning, and sleep quality, and a willingness to accept a small to modest risk of mostly self-limited and transient harms may choose a therapeutic trial, while those who place a greater value on avoiding treatment-related toxicity may decline.

Where available, a trial of a commercially-available oral cannabinoid (eg, dronabinol in the United States; nabilone where available) is reasonable. The use of smoked or vaporized cannabis (marijuana) or cannabidiol (CBD) oil for refractory cancer pain cannot be recommended. (See 'Cannabis and cannabinoids' above.)

- A trial of tizanidine, an alpha-2 adrenergic agonist, should be limited to patients who are not hemodynamically unstable, predisposed to serious hypotension, or encephalopathic from other causes. (See 'Alpha-2 adrenergic agonists' above.)

- **Neuropathic pain**

  - **Patients with depressed mood** – If neuropathic pain is associated with a significantly depressed mood, we suggest first-line therapy with an antidepressant rather than a different type of adjuvant analgesic (**Grade 2C**). For most patients we prefer an SNRI such as duloxetine. (See 'Analgesic antidepressants' above.)

  - **Others** – For most patients with neuropathic pain that is unrelated to prior chemotherapy and not associated with a depressed mood, we suggest first-line therapy with gabapentin or pregabalin rather than an antidepressant (**Grade 2C**). We generally prefer pregabalin because dose adjustments are simpler. (See 'Gabapentin and pregabalin' above.)

    For patients with chemotherapy-induced peripheral neuropathy, duloxetine is a preferred first-line agent. Specific recommendations are provided elsewhere. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy".)

  - **Refractory cases** – Patients who don't respond to the initial drug trial may be considered for trials of the alternative gabapentinoid or alternative analgesic antidepressants. Another approach is to choose the next drug from a different class (eg, trying a gabapentinoid if an antidepressant is not effective), but there is no evidence to support this practice. If an adjuvant analgesic provides meaningful, but insufficient analgesia, another drug may be added if the risks are acceptable (eg, adding low-dose desipramine to a gabapentinoid).

    Other options include a trial of oxcarbazepine or lacosamide, an alpha-2 adrenergic agonist (eg, tizanidine), or possibly a cannabinoid. For patients with focal, peripherally generated pain, a trial of a transdermal lidocaine patch is another option. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above and 'Other anticonvulsants' above and 'Topical therapies' above.)

- **Bone pain**

  - Patients with multifocal bone pain are usually managed with a nonsteroidal anti-inflammatory drug, unless they have a specific contraindication to use of these agents, and an opioid. Specific recommendations are provided separately. (See "Cancer pain management: Use of acetaminophen and nonsteroidal anti-inflammatory drugs", section on 'Indications and contraindications'.)

  - Osteoclast inhibitors are indicated, in conjunction with an opioid, in patients with symptomatic bone metastases from a variety of cancers. As adjuvant agents, there is evidence to support the analgesic potential of all osteoclast inhibitors, although benefit seems modest in most patients. (See 'Osteoclast inhibitors' above.)

  - Use of bone-targeted radiopharmaceuticals, such as radium-223, is typically reserved for the patient with multifocal bone pain that is refractory to other treatment; most of the available data are in advanced prostate cancer. (See 'Bone-targeted radiopharmaceuticals' above.)

  - Glucocorticoids may be useful in patients with opioid-refractory bone pain, especially in with the setting of advanced illness and limited prognosis, or a "pain crisis," severe and escalating pain that is not responding sufficiently to an opioid. (See 'Glucocorticoids' above.)

REFERENCES

1. Portenoy RK. A Practical Approach to Using Adjuvant Analgesics in Older Adults. J Am Geriatr Soc 2020; 68:691.
2. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness. J Pain Symptom Manage 2001; 21:338.
3. Kane CM, Mulvey MR, Wright S, et al. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: Systematic review and meta-analysis. Palliat Med 2018; 32:276.
4. Della Cuna GR, Pellegrini A, Piazzi M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients: a placebo-controlled, multicenter study. The Methylprednisolone Preterminal Cancer Study Group. Eur J Cancer Clin Oncol 1989; 25:1817.

5. Tannock I, Gospodarowicz M, Meakin W, et al. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol 1989; 7:590.
6. Mercadante SL, Berchovich M, Casuccio A, et al. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. Am J Hosp Palliat Care 2007; 24:13.
7. Popiela T, Lucchi R, Giongo F. Methylprednisolone as palliative therapy for female terminal cancer patients. The Methylprednisolone Female Preterminal Cancer Study Group. Eur J Cancer Clin Oncol 1989; 25:1823.
8. Bruera E, Roca E, Cedaro L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 1985; 69:751.
9. Bruera E, Moyano JR, Sala R, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manage 2004; 28:381.
10. Paulsen O, Klepstad P, Rosland JH, et al. Efficacy of methylprednisolone on pain, fatigue, and appetite loss in patients with advanced cancer using opioids: a randomized, placebo-controlled, double-blind trial. J Clin Oncol 2014; 32:3221.
11. Yennurajalingam S, Frisbee-Hume S, Palmer JL, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 2013; 31:3076.
12. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. Cochrane Database Syst Rev 2015; :CD010756.
13. George R, Jeba J, Ramkumar G, et al. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev 2015; :CD006716.
14. Lawton AJ, Lee KA, Cheville AL, et al. Assessment and Management of Patients With Metastatic Spinal Cord Compression: A Multidisciplinary Review. J Clin Oncol 2019; 37:61.
15. Urits I, Peck J, Orhurhu MS, et al. Off-label Antidepressant Use for Treatment and Management of Chronic Pain: Evolving Understanding and Comprehensive Review. Curr Pain Headache Rep 2019; 23:66.
16. Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. Expert Opin Pharmacother 2010; 11:2813.
17. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness

network meta-analysis. Ann Intern Med 2014; 161:639.

18. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol 2012; 52:6.
19. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain 1992; 49:205.
20. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med 2002; 162:19.
21. Mease PJ, Dundon K, Sarzi-Puttini P. Pharmacotherapy of fibromyalgia. Best Pract Res Clin Rheumatol 2011; 25:285.
22. Ferreira GE, McLachlan AJ, Lin CC, et al. Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis. BMJ 2021; 372:m4825.
23. Woolf CJ, American College of Physicians, American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004; 140:441.
24. Sindrup SH, Gram LF, Skjold T, et al. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. Clin Pharmacol Ther 1990; 47:509.
25. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992; 326:1250.
26. Sindrup SH, Bach FW, Madsen C, et al. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology 2003; 60:1284.
27. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004; 110:697.
28. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005; 119:5.
29. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006; 67:1411.
30. Matsuoka H, Iwase S, Miyaji T, et al. Additive Duloxetine for Cancer-Related Neuropathic Pain Nonresponsive or Intolerant to Opioid-Pregabalin Therapy: A Randomized Controlled Trial (JORTC-PAL08). J Pain Symptom Manage 2019; 58:645.
31. Gallagher HC, Gallagher RM, Butler M, et al. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev 2015; :CD011091.

32. Sindrup SH, Gram LF, Brøsen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain 1990; 42:135.
33. Sindrup SH, Bjerre U, Dejgaard A, et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clin Pharmacol Ther 1992; 52:547.
34. Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology 2001; 57:1583.
35. Semenchuk MR, Davis B. Efficacy of sustained-release bupropion in neuropathic pain: an open-label study. Clin J Pain 2000; 16:6.
36. Wang SM, Han C, Bahk WM, et al. Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. Chonnam Med J 2018; 54:101.
37. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013; 309:1359.
38. Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. Ther Adv Psychopharmacol 2015; 5:357.
39. Wrzosek A, Woron J, Dobrogowski J, et al. Topical clonidine for neuropathic pain. Cochrane Database Syst Rev 2015; 8:CD010967.
40. Neil MJ. Clonidine: clinical pharmacology and therapeutic use in pain management. Curr Clin Pharmacol 2011; 6:280.
41. Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. Pain 1995; 60:267.
42. Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. Pain Physician 2002; 5:422.
43. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004; 98:153.
44. Prommer E. Review article: dexmedetomidine: does it have potential in palliative medicine? Am J Hosp Palliat Care 2011; 28:276.
45. Smith HS, Barton AE. Tizanidine in the management of spasticity and musculoskeletal complaints in the palliative care population. Am J Hosp Palliat Care 2000; 17:50.
46. Semenchuk MR, Sherman S. Effectiveness of tizanidine in neuropathic pain: an open-label study. J Pain 2000; 1:285.

47. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/january-2020.html#a4.1 (Accessed on December 22, 2021).
48. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008; 9:164.
49. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004; 329:253.
50. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005; 65:812.
51. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010; 39:167.
52. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA 2003; 290:1757.
53. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9:506.
54. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013; 14:136.
55. Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. The intersection between cannabis and cancer in the United States. Crit Rev Oncol Hematol 2012; 83:1.
56. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain 2012; 13:438.
57. Lichtman AH, Lux EA, McQuade R, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. J Pain Symptom Manage 2018; 55:179.
58. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015; 313:2456.
59. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. JAMA 2015; 313:2474.
60. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain 2015; 16:1221.

61. Nugent SM, Morasco BJ, O'Neil ME, et al. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Ann Intern Med 2017; 167:319.
62. Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain 2017; 11:119.
63. Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support Palliat Care 2020; 10:14.
64. Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ 2021; 374:n1034.
65. Zeng L, Lytvyn L, Wang X, et al. Values and preferences towards medical cannabis among people living with chronic pain: a mixed-methods systematic review. BMJ Open 2021; 11:e050831.
66. Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. BMJ Open 2021; 11:e047717.
67. Zeraatkar D. Cooper MA, Agarwal A, et al. Long-term and serious harms of medical cannabi s or cannabinoids among patients with chronic pain: a systematic review of non-randomize d studies. medRxiv 2021. Preprint manuscript available online at https://www.medrxiv.org/ content/10.1101/2021.05.27.21257921v1 (Accessed on September 23, 2021).
68. Busse JW, Vankrunkelsven P, Zeng L, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ 2021; 374:n2040.
69. Furlow B. States and US Government spar over medical marijuana. Lancet Oncol 2012; 13:450.
70. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68:515.
71. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009; 34:672.
72. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010; 182:E694.
73. Montana Department of Health and Human Services. Montana Medical Marijuana Progra m. Data available online at http://www.dphhs.mt.gov/marijuanaprogram/ (Accessed on Jan uary 17, 2013).

74. Colorado Department of Public Health and Environment. The ColoradoMedical Marijuana Registry. Data available online at http://www.cdphe.state.co.us.hs/medicalmarijuana/ (Accessed on January 17, 2013).
75. Oregon Department of Human Services . The Oregon Medical Marijuana Program. Data available online at http://public.health.oregon.gov/diseasesconditions/chronicdisease/medicalmarijuanaprogram/Pages/index.aspx (Accessed on January 17, 2013).
76. Nevada Department of Health and Human Services. Medical Marijuana Program. Data available online at http://health.nv.gov/BudgetDocuments/2012-2013/MMPWHITEPAPR_FY11.pdf.
77. Bonn-Miller MO, Loflin MJE, Thomas BF, et al. Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA 2017; 318:1708.
78. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014; 370:2219.
79. Owen KP, Sutter ME, Albertson TE. Marijuana: respiratory tract effects. Clin Rev Allergy Immunol 2014; 46:65.
80. Patel S, Williams JW Jr, Wallace RB. What We Do (and Don't) Know About the Health Effects of Cannabis and Whether Marijuana Is Medicine. Ann Intern Med 2017; 166:747.
81. Ghasemiesfe M, Ravi D, Vali M, et al. Marijuana Use, Respiratory Symptoms, and Pulmonary Function: A Systematic Review and Meta-analysis. Ann Intern Med 2018; 169:106.
82. The National Academies of Science, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. 2017. https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state (Accessed on May 10, 2021).
83. Incze MA, Kelley AT, Singer PM. Heterogeneous State Cannabis Policies: Potential Implications for Patients and Health Care Professionals. JAMA 2021; 326:2363.
84. Hardy J, Greer R, Huggett G, et al. Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD). J Clin Oncol 2023; 41:1444.
85. Anderson SP, Zylla DM, McGriff DM, Arneson TJ. Impact of Medical Cannabis on Patient-Reported Symptoms for Patients With Cancer Enrolled in Minnesota's Medical Cannabis Program. J Oncol Pract 2019; 15:e338.
86. Pasha AK, Clements CY, Reynolds CA, et al. Cardiovascular Effects of Medical Marijuana: A Systematic Review. Am J Med 2021; 134:182.

87. Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev 2014; :CD010958.
88. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol 1995; 37:246.
89. Gammaitoni AR, Alvarez NA, Galer BS. Pharmacokinetics and safety of continuously applied lidocaine patches 5%. Am J Health Syst Pharm 2002; 59:2215.
90. Gabra BH, Abidi MH, Al-Khadimi Z, et al. Systemic absorption of topical lidocaine in a bone marrow transplant recipient with hepatic sinusoidal obstruction syndrome. Am J Health Syst Pharm 2011; 68:135.
91. De Martin S, Orlando R, Bertoli M, et al. Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. Clin Pharmacol Ther 2006; 80:597.
92. Stow PJ, Glynn CJ, Minor B. EMLA cream in the treatment of post-herpetic neuralgia. Efficacy and pharmacokinetic profile. Pain 1989; 39:301.
93. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14:162.
94. Haanpää M, Cruccu G, Nurmikko TJ, et al. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. Eur J Pain 2016; 20:316.
95. Sommer C, Cruccu G. Topical Treatment of Peripheral Neuropathic Pain: Applying the Evidence. J Pain Symptom Manage 2017; 53:614.
96. Jones VM, Moore KA, Peterson DM. Capsaicin 8% topical patch (Qutenza)--a review of the evidence. J Pain Palliat Care Pharmacother 2011; 25:32.
97. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2009; :CD007393.
98. Burness CB, McCormack PL. Capsaicin 8 % Patch: A Review in Peripheral Neuropathic Pain. Drugs 2016; 76:123.
99. Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017; 5:CD008609.
100. Ho KY, Huh BK, White WD, et al. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clin J Pain 2008; 24:51.
101. McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. Br J Clin Pharmacol 2000; 49:574.

102. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer 2011; 19:833.

103. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. J Clin Oncol 2020; 38:3325.

104. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes -an evidence based review. Toxicon 2018; 147:120.

105. Bach CA, Wagner I, Lachiver X, et al. Botulinum toxin in the treatment of post-radiosurgical neck contracture in head and neck cancer: a novel approach. Eur Ann Otorhinolaryngol Head Neck Dis 2012; 129:6.

106. Wang L, Lei QS, Liu YY, et al. A case report of the beneficial effects of botulinum toxin type A on Raynaud phenomenon in a patient with lung cancer. Medicine (Baltimore) 2016; 95:e5092.

107. Rostami R, Mittal SO, Radmand R, Jabbari B. Incobotulinum Toxin-A Improves Post-Surgical and Post-Radiation Pain in Cancer Patients. Toxins (Basel) 2016; 8.

108. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132:237.

109. Paice JA, Portenoy R, Lacchetti C, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34:3325.

110. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med 2011; 25:553.

111. Jongen JL, Huijsman ML, Jessurun J, et al. The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. J Pain Symptom Manage 2013; 46:581.

112. Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study. Ann Intern Med 2018; 169:732.

113. Gomes T, Juurlink DN, Antoniou T, et al. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med 2017; 14:e1002396.

114. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin (Accessed on January 23, 2020).

115. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol 2004; 22:2909.
116. Mishra S, Bhatnagar S, Goyal GN, et al. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care 2012; 29:177.
117. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. J Pain Symptom Manage 2007; 34:183.
118. Jiang J, Li Y, Shen Q, et al. Effect of Pregabalin on Radiotherapy-Related Neuropathic Pain in Patients With Head and Neck Cancer: A Randomized Controlled Trial. J Clin Oncol 2019; 37:135.
119. Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Med 2010; 11:456.
120. Hepner S, Claxton R. Anti-epileptic drugs for pain #271. J Palliat Med 2013; 16:799.
121. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014; :CD005451.
122. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane Database Syst Rev 2013; :CD010567.
123. Zhou M, Chen N, He L, et al. Oxcarbazepine for neuropathic pain. Cochrane Database Syst Rev 2017; 12:CD007963.
124. Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. Pain 2014; 155:2263.
125. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2012; 2012:CD009318.
126. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. Cochrane Database Syst Rev 2007; :CD006044.
127. Bendaly EA, Jordan CA, Staehler SS, Rushing DA. Topiramate in the treatment of neuropathic pain in patients with cancer. Support Cancer Ther 2007; 4:241.
128. Wiffen PJ, Derry S, Lunn MP, Moore RA. Topiramate for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2013; :CD008314.
129. Yajnik S, Singh GP, Singh G, Kumar M. Phenytoin as a coanalgesic in cancer pain. J Pain Symptom Manage 1992; 7:209.

130. Hardy JR, Rees EA, Gwilliam B, et al. A phase II study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. J Pain Symptom Manage 2001; 21:204.
131. Hugel H, Ellershaw JE, Dickman A. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. J Pain Symptom Manage 2003; 26:1073.
132. Garzón-Rodríguez C, Casals Merchan M, Calsina-Berna A, et al. Lidocaine 5 % patches as an effective short-term co-analgesic in cancer pain. Preliminary results. Support Care Cancer 2013; 21:3153.
133. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005; :CD003345.
134. Buchanan DD, J MacIvor F. A role for intravenous lidocaine in severe cancer-related neuropathic pain at the end-of-life. Support Care Cancer 2010; 18:899.
135. Jackson K, Ashby M, Howell D, et al. The effectiveness and adverse effects profile of "burst" ketamine in refractory cancer pain: The VCOG PM 1-00 study. J Palliat Care 2010; 26:176.
136. Jackson K, Ashby M, Martin P, et al. "Burst" ketamine for refractory cancer pain: an open-label audit of 39 patients. J Pain Symptom Manage 2001; 22:834.
137. Ben-Ari A, Lewis MC, Davidson E. Chronic administration of ketamine for analgesia. J Pain Palliat Care Pharmacother 2007; 21:7.
138. Prommer EE. Ketamine for pain: an update of uses in palliative care. J Palliat Med 2012; 15:474.
139. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 2000; 20:246.
140. Lauretti GR, Lima IC, Reis MP, et al. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. Anesthesiology 1999; 90:1528.
141. Yang CY, Wong CS, Chang JY, Ho ST. Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 1996; 43:379.
142. Lauretti GR, Gomes JM, Reis MP, Pereira NL. Low doses of epidural ketamine or neostigmine, but not midazolam, improve morphine analgesia in epidural terminal cancer pain therapy. J Clin Anesth 1999; 11:663.
143. Salas S, Frasca M, Planchet-Barraud B, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in

palliative care. J Palliat Med 2012; 15:287.

144. Hardy J, Quinn S, Fazekas B, et al. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. J Clin Oncol 2012; 30:3611.

145. Ishizuka P, Garcia JB, Sakata RK, et al. Assessment of oral S+ ketamine associated with morphine for the treatment of oncologic pain. Rev Bras Anestesiol 2007; 57:19.

146. Bell RF, Eccleston C, Kalso EA. Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017; 6:CD003351.

147. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med 2018; 43:521.

148. Quibell R, Fallon M, Mihalyo M, et al. Ketamine. J Pain Symptom Manage 2015; 50:268.

149. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth 2011; 58:911.

150. Schwenk ES, Goldberg SF, Patel RD, et al. Adverse Drug Effects and Preoperative Medication Factors Related to Perioperative Low-Dose Ketamine Infusions. Reg Anesth Pain Med 2016; 41:482.

151. Krystal JH, D'Souza DC, Karper LP, et al. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 1999; 145:193.

152. Okamoto Y, Tsuneto S, Tanimukai H, et al. Can gradual dose titration of ketamine for management of neuropathic pain prevent psychotomimetic effects in patients with advanced cancer? Am J Hosp Palliat Care 2013; 30:450.

153. Mercadante S, Caruselli A, Casuccio A. The use of ketamine in a palliative-supportive care unit: a retrospective analysis. Ann Palliat Med 2018; 7:205.

154. Loveday BA, Sindt J. Ketamine Protocol for Palliative Care in Cancer Patients With Refractory Pain. J Adv Pract Oncol 2015; 6:555.

155. Marchetti F, Coutaux A, Bellanger A, et al. Efficacy and safety of oral ketamine for the relief of intractable chronic pain: A retrospective 5-year study of 51 patients. Eur J Pain 2015; 19:984.

156. Chizh BA, Headley PM. NMDA antagonists and neuropathic pain--multiple drug targets and multiple uses. Curr Pharm Des 2005; 11:2977.

157. Yomiya K, Matsuo N, Tomiyasu S, et al. Baclofen as an adjuvant analgesic for cancer pain. Am J Hosp Palliat Care 2009; 26:112.

158. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf (Accessed on July 25, 2023).

159. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012; 13:e58.

160. O'Carrigan B, Wong MH, Willson ML, et al. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2017; 10:CD003474.

161. Hoskin P, Sundar S, Reczko K, et al. A Multicenter Randomized Trial of Ibandronate Compared With Single-Dose Radiotherapy for Localized Metastatic Bone Pain in Prostate Cancer. J Natl Cancer Inst 2015; 107.

162. Hendriks LE, Hermans BC, van den Beuken-van Everdingen MH, et al. Effect of Bisphosphonates, Denosumab, and Radioisotopes on Bone Pain and Quality of Life in Patients with Non-Small Cell Lung Cancer and Bone Metastases: A Systematic Review. J Thorac Oncol 2016; 11:155.

163. Cleeland CS, Body JJ, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013; 119:832.

164. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res 2012; 18:4841.

165. Patrick DL, Cleeland CS, von Moos R, et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer 2015; 23:1157.

166. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010; 28:5132.

167. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377:813.

168. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011; 29:1125.

169. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update. J Clin Oncol 2017; 35:3978.

170. Fabregat C, Almendros S, Navarro-Martin A, Gonzalez J. Pain Flare-Effect Prophylaxis With Corticosteroids on Bone Radiotherapy Treatment: A Systematic Review. Pain Pract 2020; 20:101.

Topic 2815 Version 103.0

GRAPHICS

Adjuvant analgesics used for cancer pain

Category based on conventional use	Class	Subclass	Drugs
Multipurpose analgesics	Glucocorticoids	–	Dexamethasone, prednisone, methylprednisone
	Antidepressants	Tricyclic	Amitriptyline, desipramine, nortriptyline
		SNRIs	Duloxetine, minalcipran desvenlafaxine
		SSRIs	Paroxetine, citalopram
		Other	Buproprion
	Alpha-2 adrenergic agonists	–	Tizanidine, clonidine
	Cannabinoids	–	Dronabinol, nabilone, nabiximols
	Topical analgesics	–	Local anesthetics, lidocaine, capsaicin, tricyclic antidepressants NSAIDs, others
	Botulinum toxin injections	–	–
Used for neuropathic pain	All multipurpose analgesics	Refer to above	Refer to above
	Antiseizure medications	–	Gabapentin, pregabalin valproate, phenytoin, carbamazepine, oxcarbazepine, topiramate, lamotrigine
	Sodium channel blockers	Sodium channel modulator	Lacosamide
		Sodium channel blocker	Mexiletine, intravenous lidocaine

	NMDA receptor antagonists	–	Ketamine, memantine, dextromethorphan, amantadine
	GABA agonists	$GABA_a$ agonists	Clonazepam
		$GABA_b$ agonists	Baclofen
Used for bone pain	Osteoclast inhibitors	Bisphosphonates	Pamidronate, zolendronate, ibandronate
		–	Calcitonin
		RANKL inhibitor	Denosumab
	Radiopharmaceuticals	–	Strontium-89, samarium-153, radium-223
	NSAIDs, glucocorticoids	–	–
Used for bowel obstruction	Anticholinergic drugs	–	Scopolamine, atropine, glycopyrrolate
	Somatostatin analog	–	Octreotide
	Glucocorticoids	–	–

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; NSAID: Nonsteroidal antiinflammatory drugs; NMDA: N-methyl-D-aspartate; GABA: gamma-aminobutyric acid; RANKL: receptor activator of nuclear factor kappa B ligand.

Graphic 80423 Version 3.0

Therapeutic dose ranges for commonly used adjuvant analgesics

Category based on conventional use	Class	Drugs	Usual starting dose	Usual effective dose range*
Multipurpose analgesics	Glucocorticoids	Dexamethasone	Varies	1 to 2 mg twice daily, orally or IV
		Prednisone	Varies	5 to 10 mg twice daily
	Antidepressants	Desipramine	10 to 25 mg at bedtime	50 to 150 mg at bedtime
		Duloxetine	20 to 30 mg daily	60 to 120 mg daily[¶]
		Bupropion	75 mg twice daily	300 to 450 mg daily[Δ]
		Venlafaxine, sustained release	75 mg once daily	150 to 225 mg daily
		Nortriptyline	10 to 25 mg at bedtime	50 to 150 mg at bedtime
	Alpha-2 adrenergic agonists	Tizanidine	1 to 2 mg at bedtime	2 to 8 mg twice daily
Used for neuropathic pain	Antiseizure medications	Gabapentin	100 to 300 mg twice daily	300 to 1200 mg three times daily
		Pregabalin	50 to 75 mg twice daily[◇]	150 to 300 mg twice daily
	GABA agonists	Clonazepam	0.5 mg at bedtime	0.5 to 3 mg daily
Used for bone pain	Osteoclast inhibitors	Pamidronate	–	60 to 90 mg monthly, IV
		Zoledronic acid	–	4 mg monthly, IV
		Denosumab	–	120 mg monthly, subcutaneously
Used for bowel obstruction	Anticholinergic drugs	Glycopyrrolate	0.1 mg daily	0.1 to 0.2 mg three times daily, subcutaneously
	Somatostatin analogue	Octreotide	Varies	0.1 to 0.3 mg twice daily,

				subcutaneously

IV: intravenous; GABA: gamma-aminobutyric acid.

* All doses shown are for adult patients, oral administration, unless otherwise noted.

¶ Randomized trials conducted in patients with diabetic peripheral neuropathy suggest no additional efficacy from 120 mg daily versus 60 mg daily.

Δ Bupropion doses ≥150 mg should be sustained release.

◇ Medically frail patients and those with significantly impaired kidney function are started at 25 mg once daily and titrated more gradually.

Graphic 82318 Version 7.0

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an antiinflammatory effect¶. The typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

---

* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

¶ The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is not used clinically as an antiinflammatory agent.

Data from:

1. *Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed, Brunton LL, Chabner BA, Knollmann BC (Eds), McGraw-Hill Education 2011.*
2. *Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 2013, 9:30.*

Graphic 64138 Version 23.0

Overview and visual summary of expert guideline recommendation for non-inhaled medical cannabis or cannabinoids for chronic pain

Visual summary of recommendation

Population

These recommendations apply only to people with these characteristics:

All patients living with moderate to severe chronic pain

Applies to people with:

- ✔ Cancer and non-cancer pain
- ✔ Neuropathic pain, nociceptive pain, and nociplastic pain

May or may not apply to:

- ? Paediatric populations
- ? Veterans
- ? Patients with concurrent mental illness
- ? Patients receiving disability benefits or involved in litigation

Does not apply to:

- ✖ Inhaled medical cannabis
- ✖ Recreational cannabis
- ✖ Patients receiving end of life care

Recommendation

Standard care		Cannabis
No trial of medical cannabis or cannaninoids	or	Standard care plus a trial of non-inhaled medical cannabis or cannabinoids
Strong / Weak		Weak / Strong

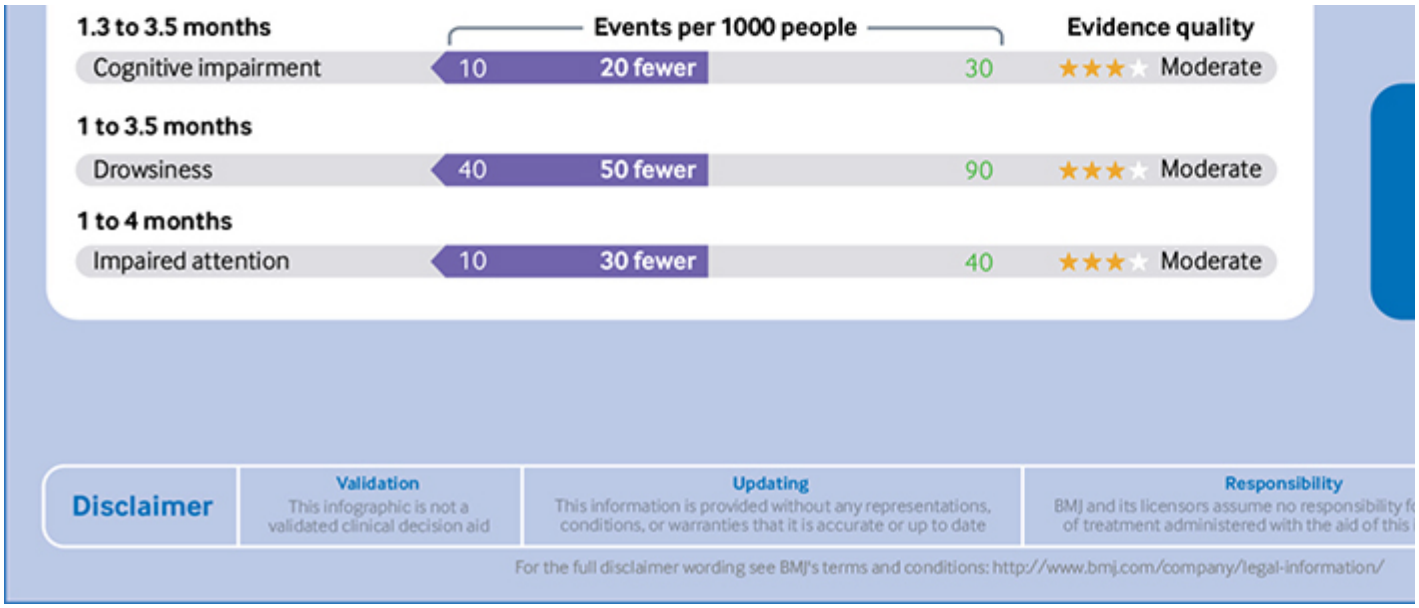
> If standard care is not sufficient, we suggest offering a trial of non-inhaled medical cannabis or cannabinoids

Evidence profile potential benefits

Favours standard care | No important difference | Favours cannabis

	Events per 1000 people			Evidence quality
1 to 4 months				
Reduction in pain	520	100 more	620	★★★☆ Moderate
Improved physical function	280	40 more	320	★★★★ High
Improved emotional function	310	No important difference	330	★★★★ High
1 to 3.5 months				
Improved role function	410	No important difference	410	★★★★ High
Improved social function	390	No important difference	380	★★★★ High
1.3 to 3.5 months				
Improved sleep quality	480	60 more	540	★★★★ High

Evidence profile potential short term harms



Reproduced with permission from: Busse JW, Vanrunkelsven P, Zeng L, et al. Medical Cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ 2021; 374:n2040. Copyright © 2021 BMJ Publishing Group Ltd.

Graphic 132771 Version 1.0

Topical analgesics for treatment of superficial painful conditions

Topical analgesic	Usual dose (adult)	Characteristics
Topical nonsteroidal antiinflammatory drugs (NSAIDs)*		
Diclofenac topical gel (1%)	Knees: Rub in 4 g of gel to affected knee(s) three to four times daily. Hands: Rub in 2 g of gel to affected joint(s) three to four times daily. Maximum 16 g per joint per day; 32 g total per day.	▪ Applies to all topically administered NSAIDs: • Useful for treatment of musculoskeletal pain and osteoarthritis of superficial joints (eg, wrist, knee, hand) as an alternative to systemic therapy • Minimal systemic absorption • Safety data are reassuring despite label warnings on United States products • Local skin reactions include rash, itch, or burning (some products contain propylene glycol, a potential irritant and rarely an allergen) • Refer to topic review on initial pharmacologic therapy of osteoarthritis
Diclofenac topical patch (1.3%)	Apply one patch to most painful area one to two times daily (refer to product-specific instructions).	
Diclofenac topical solution drops (1.5%)	Knees: Rub in 40 drops to affected knee(s) up to four times daily.	
Diclofenac topical solution pump (2%)	Knees: Rub in two pump actions to affected knee(s) up to two times daily.	
Ibuprofen topical gel (5, 10%); not available in United States	Knees or hands: Rub in dose (depends on joint size and location) up to four times daily; refer to product-specific information for detail.	
Ketoprofen topical gel (2.5%); not available in United States	Knees or hands: Rub in 2 to 4 g of gel two to four times daily (maximum 15 g of gel per day); refer to product-specific information for detail.	
Topical capsaicin¶		
Capsaicin creams, gels, liquids, or lotions (0.025 to 0.1%)	Rub in a small amount (pea sized) one to four times daily; the preparation most often studied in osteoarthritis was 0.025% cream.	▪ Useful for treatment of osteoarthritis pain and postherpetic neuralgia as an adjunct or alternative to systemic analgesics ▪ Local irritation may be intolerable ▪ Refer to topic review on initial pharmacologic therapy of osteoarthritis
Capsaicin topical patches (0.025 to 0.05%)	Apply one patch to affected area for up to eight hours (maximum four patches per day).	

Capsaicin topical patch (high concentration 8%)	Postherpetic neuralgia (single treatment): Apply up to four patches to the most painful area for 60 minutes. Treatment may be repeated after three months.	▪ Potential option for local pain relief in postherpetic neuralgia ▪ High-concentration patch must be administered by a health care professional and monitored for up to two hours after treatment ▪ Pretreatment with a local anesthetic (eg, lidocaine) is necessary ▪ After application, local cooling measures can decrease discomfort ▪ Local pain and irritation may be intolerable ▪ Refer to topic review on postherpetic neuralgia
Topical lidocaine		
Lidocaine topical patch (5%)	One to three patches applied for up to 12 hours in any 24-hour period.	▪ Low (3 to 5%) systemic absorption through intact skin ▪ Useful for local relief of pain (eg, due to postherpetic neuralgia) in limited areas of intact skin as an adjunct or alternative to systemic analgesics
Lidocaine topical creams, ointments, and gels (2 to 4%)	Apply a thin film two to four times daily (refer to product-specific instructions).	▪ Useful for local relief of minor superficial skin irritation and pain
Lidocaine topical cream (5%)	Apply a thin film three to four times daily (maximum six times daily).	▪ Useful for local relief of anorectal pain and itching

Topical analgesic therapies are moderately effective and useful in combination with systemic therapies for reducing medication load and side effects, and potentially, as monotherapy for adults with localized pain and contraindications to systemic therapies.

---

* For patients already on oral NSAIDs, topical therapies are generally not recommended because they are unlikely to provide additional pain relief. Gel measurements from tubes are approximate.

¶ Pain relief usually begins within the first week of treatment, and full effect is seen with regular application over approximately four weeks. Topical capsaicin should not come in contact with mucous membranes, abraded skin, eyes, or genital areas.

Data from:

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

2. The electronic medicines compendium (emc) DataPharm Ltd. Surrey United Kingdom (https://www.medicines.org.uk/emc/).

Graphic 93846 Version 15.0

Contributor Disclosures

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.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy