INTRODUCTION — Burns can be extremely painful. Pain management, which includes pharmacologic and nonpharmacologic approaches, is a central component of the complex issues involved in treating patients with burns. Management of anxiety is also important given that high levels of anxiety can increase the perception of pain. Poor pain and anxiety management can also contribute to delayed wound healing [1]. Despite advances in burn care, inadequate burn pain management still exists during both the acute and rehabilitation phases of care [2]. Burn pain is among the most common causes of distress during the first year after discharge [3,4]. Burn pain management is based upon tradition, personal bias, and/or institutional preference rather than based upon scientific approaches [5].

An overview of pharmacologic and nonpharmacologic options for the management of burn pain is reviewed here. Emergency care and local management of burns and pain are discussed elsewhere. (See "Emergency care of moderate and severe thermal burns in adults" and "Emergency care of moderate and severe thermal burns in children" and "Local treatment of burns: Topical antimicrobial agents and dressings" and "Paradigm-based treatment approaches for burn pain control".)

CHARACTERISTICS OF BURN PAIN — All burns are painful initially [6]. Burn pain varies greatly from patient to patient, shows substantial fluctuation over the hospitalization course, and can be unpredictable due to the complex interaction of anatomic, physiologic, psychosocial, and premorbid behavior issues. Burn patients typically report pain as being severe or excruciating, despite receiving opioid analgesics.

Burn pain also varies depending upon depth of burn (figure 1) (see "Classification of burns"):

- Superficial partial thickness burns result in hyperalgesia and mild to moderate pain. They are the most painful burns immediately following the injury. These burns damage only the outer layers of the skin.
- Moderate partial thickness burns are associated with marked hyperalgesia, and produce moderate to severe pain. Burns at this depth injure and/or inflame sensory receptors in the dermis.
- Deep partial thickness to full thickness burns are typically characterized by an absence of pain. Hyperalgesia to cutaneous stimulation is uncommon. Acute pain is typically minimal, but can be variable, and is universally present with respect to the transition zone between burned and unburned skin. The dermis is completely destroyed, including its sensory and vascular structures. There is little to no response to sharp stimuli, yet patients complain of a deep aching pain related to the inflammatory response.

BURN PAIN ASSESSMENT TECHNIQUES — Pain assessment tools must be practical, reliable, and valid, and must be able to assess three dimensions of pain: pain intensity, behavioral reactions, and physiologic reactions. A variety of pain measurement tools have been used with adult and pediatric burn patients. However, there are no randomized trials that have identified an optimal assessment technique for burn patients. The key is to choose an instrument and use it consistently. The most common tools used for adults and children with burn pain include verbal adjective scales, numeric written or visual analog scales, pain assessment in dementia scales, FACES, and FLACC (Face, Legs, Activity, Cry, Consolability) [6-11].
**Adults** — The more common tools for assessing post burn pain in adults are the adjective scales, which allow a patient to describe the severity of pain in words, such as “none, mild, moderate, or severe” or “no pain, mild, discomforting, distressing, horrible, or excruciating pain” (figure 2) [10]. An alternative to the verbal description of pain is the numeric scale, which allows a patient to describe the pain on a scale of increasing severity typically from 0 to 10 (figure 3) [9]. The numeric scale is administered to the patient verbally or written as a visual analog scale (figure 4). Pain assessment can be challenging in the burned and demented patient. The Pain Assessment in Advanced Dementia Scale, an observational scoring instrument, is a simple to administer valid and reliable instrument (table 1) [11]. (See "Pain control in the critically ill adult patient", section on 'Goals of pain control'.)

**Children** — The measurement of children's pain is much more complex than it is for adults, especially for preverbal children. Typical physiologic indicators, such as heart rate, respiratory rate, and blood pressure are unreliable in measuring a child’s pain since all are affected by a variety of stressors related to the burn injury [6,12]. (See "Evaluation and management of pain in children", section on 'Assessment of pain severity and cognition'.)

Behavior scales have been devised to measure pain by providing standardized instructions and guidelines for observing behaviors thought to be specific to pain. Facial expression may be the most consistent infant indicator of pain. Observational scales have been developed that are multidimensional and include length of cry, facial expressions, and behavioral states [4]. These scales are easier to use and allow an observer to assess pain as either present or absent without further quantification. The FLACC (Faces Legs Activity Cry Consolability scale) is the most widely used observer rating scale in preverbal children (table 2) [7,13].

Simple self-report pain scales can be used with preschool children. There is no evidence that any one of these scales is more reliable than the other, hence, it is best to select one that the evaluator prefers and it should be used consistently. When self-report scales are used in conjunction with observational scales, a practitioner may develop a better appreciation of the intensity of the child’s response to burn pain and the effectiveness of pain management. The following are examples of pain scales that are commonly used with children:

- The Wong-Baker FACES Pain Scale is designed for children three years and older (figure 5) [8]. This pain scale uses drawings of faces displaying varying degrees of pain and discomfort. Each face communicates a level of pain intensity and the child is asked to choose the face that most accurately describes their pain level.

- The OUCHER scale includes a picture scale for very young children and a numerical scale that can be used in children over five years old [14]. There are different versions that can be used for children of various races, and an example is shown for a Caucasian boy (figure 6).

**PHARMACOLOGIC TREATMENT OPTIONS** — Pharmacologic agents used to treat burn pain include opioid analgesics, nonopioid analgesics, anxiolytics, and anesthetics. The type of medication used is determined by the severity of pain, the anticipated duration of pain, and intravenous (IV) access. These medications have variable durations of action, particularly in burn patients, and should be titrated to meet the needs of the patient in each clinical setting [15].

Pharmacologic techniques should provide near-constant plasma levels of analgesics through regularly scheduled administration of long-acting oral opioids (eg, methadone), or continuous IV opioid infusion (eg, morphine) in patients unable to take oral medications. Regularly scheduled benzodiazepines (eg, lorazepam) may have added value in patients with significant anxiety that contributes to their pain experience.

A severe burn injury results in physiologic changes that may alter the pharmacokinetic and pharmacodynamic response to drugs in inconsistent ways, hence deviation from the usual doses may be necessary to avoid toxicity or decreased efficacy [16]. The tables linked to this topic provide dosages of opioids and nonopioid analgesics as recommended for patients without serious pathophysiologic and metabolic changes without altered drug clearance. These dosages serve as a reference point for administering pharmacologic agents to burned patients. Medications may be more potent and
have a prolonged effect in the burn patient. Monitoring of the airway, breathing, and circulation is necessary, particularly when intravenous drugs are administered. (See "Hypermetabolic response to severe burn injury: Recognition and treatment").

**Opioid analgesics** — Opioid analgesics, the most common type of medication used for acute pain relief, are potent and provide a dose dependent degree of sedation important during burn wound care procedures (table 3 and table 4) [4]. Burn pain should be treated aggressively and there is no clear evidence that the use of opioids during acute burn pain management increases the likelihood of opioid dependency [17]. A review of intravenous opioid analgesia for adults and children is discussed in detail elsewhere. (See "Evaluation and management of pain in children", section on 'Opioids' and "Pain control in the critically ill adult patient" and "Procedural sedation in adults", section on 'Medications'.)

Opioids can be administered intravenously or orally, depending on IV access, gastrointestinal function, and the patient’s ability to cooperate. For severe pain, the optimal route of administration is IV, which provides faster pain relief and can be titrated to meet the individual needs of the patient.

Patient-controlled analgesia (PCA) with IV opioids offers the burn patient a safe and efficient method of achieving more flexible analgesia, provided the patient is alert and competent to use the device (table 5) [18]. (See "Management of acute perioperative pain", section on 'Patient-controlled analgesia'.) Studies comparing PCA opioid use to other routes of administration in the burn population have shown positive, but limited benefits of PCA.

Oral or gastrointestinal administration of opioids via an enteral tube provides potent pain relief with rapid onset and short duration of action, and requires minimal monitoring. Oral transmucosal administration is particularly helpful for performing burn dressing changes in children [19,20].

Intramuscular opioid administration is not recommended for use in burn patients. The injections are painful, they need to be repeated frequently, and the absorption is variable due to compartmental fluid shifts. (See "Emergency care of moderate and severe thermal burns in adults", section on 'Fluid resuscitation' and "Emergency care of moderate and severe thermal burns in children", section on 'Fluid resuscitation'.)

**Nonopioid analgesics** — Nonopioid analgesics, such as dexmedetomidine and ketamine, provide short-term effective analgesia and sedation that may be helpful for limited burn debridement and/or dressing changes in adults and children. Dexmedetomidine provides sedation, anxiolysis, and analgesia for burned children, with less respiratory depression than other sedatives [21-24]. Ketamine has a long history of use in burn-injured patients, particularly for procedural wound care pain. Studies suggest it is both an effective and safe analgesic in adult [25] and pediatric [26] patients with burns. (See "Procedural sedation in adults" and "Pharmacologic agents for pediatric procedural sedation outside of the operating room").

Other nonopioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS), provide mild analgesia and are best suited to treat minor burn pain in the outpatient setting (table 6) [27]. Oral NSAIDs and acetaminophen exhibit a ceiling effect in their dose-response relationship, rendering them unsuitable for the treatment of severe burn pain. There are no high quality data from randomized trials that have determined the optimal nonopioid analgesic for burn patients. The mechanism of action and therapeutic use of NSAIDS is discussed in detail elsewhere. (See "NSAIDs: Therapeutic use and variability of response in adults").

**Anxiolytics** — Anxiety is a common consequence of burns, due to the need for aggressive surgical treatment and debridement of the wounds, and the persistent and repetitive qualities of background and procedural burn pain. The recognition that anxiety can exacerbate acute pain has led to the common practice of using anxiolytic drugs in combination with opioid analgesics, a practice that has become more widespread in burn centers in the past three decades [28]. This practice is particularly useful in premedicating patients for wound care, due to the anticipatory anxiety experienced by these patients prior to and during such procedures.
Benzodiazepine therapy improved postprocedure pain scores in burn patients (table 7). A trial that randomly assigned 79 burn patients to receive lorazepam 1 mg or placebo in addition to their standard opioid analgesics found no difference between groups in pain scores, except in patients with high baseline pain [29]. In high baseline pain patients, lorazepam significantly reduced VAS pain score ratings (54.3 versus 69.1).

Antipsychotic medications are also an option for management of anxiety and agitation associated with burn pain and treatment [30].

- First generation antipsychotics (eg, haloperidol) are used adjunctively for treatment or prevention of hyperactive delirium and agitation in critically ill patients. (See "Sedative-analgesic medications in critically ill adults: Properties, dosage regimens, and adverse effects", section on 'Antipsychotics'.)

- Second generation antipsychotics (eg, quetiapine) are increasingly used for treating various anxiety disorders and may be useful in combination with a benzodiazepine for managing anxiety and improving sleep in burn patients. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Anesthetics — General, neuraxial, targeted nonneuraxial, and regional anesthetics are useful in managing burn pain in various clinical settings. The specific types and administration of anesthesia are discussed in detail elsewhere. (See "Anesthesia for burn patients".)

**General or deep sedation** — A general anesthetic or deep sedation provides relief of relatively brief, intense pain that would be experienced during a procedure, such as skin grafting, extensive wound debridement, or dressing changes that occur outside of the operating room. While the risks of complications following a general anesthetic are typically low in healthy individuals, burn patients have metabolic, physiologic, and thermoregulatory abnormalities as well as possible inhalation injuries that are associated with increased risk of complications of perioperative hypothermia, hypoxemia, and abnormal responses to some anesthetic agents and to both depolarizing and nondepolarizing muscle relaxants [31]. As an example, propofol clearance and volume of distribution are increased in patients with major burns, and may require larger bolus and/or infusion doses to maintain therapeutic plasma drug concentrations [32].

Inhaled nitrous oxide is an anesthetic agent that can be safely administered and provides effective analgesia without loss of consciousness (ie, moderate sedation) for moderately painful procedures. It can be used for the treatment of burn pain, typically as a 50 percent mixture in 50 percent oxygen, and self-administered by an awake, cooperative, and spontaneously breathing patient via a mouthpiece or mask [27,33,34].

Full anesthetic care capabilities have been extended outside the operating room into specialized, high volume burn center intensive care units [35,36]. Drugs, such as intravenously administered propofol and remifentanil and inhaled sevoflurane, with rapid onset and short duration of action, rapid recovery, and few side effects have facilitated burn care and pain management in the patient’s hospital bed without transporting the patient to the operating room. The occasional provision of brief, dense analgesia/anesthesia (eg, general anesthesia or deep sedation) should be administered in a comprehensively monitored setting by medical professionals specifically trained to provide the service. When administered in a controlled environment, a general anesthesia or deep sedation is safe and efficient, both in terms of allowing wound care (eg, debridement of facial burns in children) to proceed rapidly, and in terms of cost-effective use of the operating room only for true surgical burn care procedures.

**Regional** — Regional anesthesia is achieved by injecting a local anesthetic agent (eg, bupivacaine, lidocaine) around a nerve to block the sensory stimulation from that area innervated by the nerve. A regional anesthesia is particularly useful for procedures and burn pain relief involving the extremities. The most common nerve groups accessible for a nerve block include the brachial plexus (interscalene block, infraclavicular block, axillary block), the sciatic nerve, and the femoral nerve. (See "Overview of anesthesia and anesthetic choices" and "Overview of peripheral nerve blocks".)
Neuraxial — Neuraxial anesthesia is the administration of an anesthetic agent (e.g., bupivacaine, lidocaine) and/or opioid analgesics via a spinal or epidural catheter with the goal of providing background, procedural, and postoperative pain relief. This procedure has only been anecdotally used in burn patients but theoretically has the advantage of providing an autonomic sympathectomy and peripheral dilatation [37]. A major drawback to the use of neuraxial anesthesia is the potential colonization of the indwelling catheter, particularly if inserted through burned skin, and the associated risks of meningitis and epidural abscess formation [38].

Targeted non-neuraxial blockade — In contrast to neuraxial anesthesia, targeted non-neuraxial regional blockade is relatively easy to perform and carries minimal risks [39,40]. Examples of non-neuraxial nerve block include the fascia iliaca compartment blockade (FICB) and lateral femoral cutaneous nerve block, which can be used for lower extremity analgesia following skin graft harvesting [39-41].

NONPHARMACOLOGIC TREATMENT OPTIONS — Nonpharmacologic treatments should be complementary to pharmacologic approaches when treating pain and anxiety in the burn patient. Empirical evidence for the efficacy of nonpharmacologic treatments has been reported with burn pain, particularly when used as an adjunct to opioid analgesics [4].

A number of nonpharmacologic approaches are available. In choosing the most effective approach, the team should be guided by the manner in which the patient typically responded to prior stressful medical procedures, if possible. Such responses lie on a continuum ranging from giving up control to the health care professional and desiring little information, to seeking out as much information as possible and actively participating in care [42]. The following examples illustrate the types of coping styles to burn and procedural pain:

- Avoidance — Those burn patients who wish to give up control to the health care professional have a tendency toward cognitive avoidance, or an avoidance style of coping mechanism. They will likely use various types of distraction techniques to avoid the painful stimuli.
- Approach — Those burn patients who seek out information about the procedure and attempt to participate and not relinquish control have an “approach” style of coping mechanism. These patients often find distraction techniques distressing as trying to ignore a procedure may serve to relinquish too much control.

It is important to note that both coping styles can be adaptive and it is best for the burn care team to support an individual’s coping style rather than try to change the natural response. Patients may also change their coping style depending on the procedure. As an example, a patient may find it is easier to use distraction techniques for short procedures such as receiving injections, whereas they are more comfortable attending to details of their long wound care sessions and participating when possible. Patients may also change their coping style as they become more familiar and comfortable with the environment.

Avoidance techniques — Avoidance interventions are designed to psychologically distract or distance the patient from the pain. The Multiple Resource Theory of Attention suggests that diverting attention towards a nonpainful stimulus may lessen the intensity of perceived pain [43]. The four interventions in the avoidance category include distraction, guided imagery, hypnotic analgesia, and virtual reality [4]. The nonpharmacological techniques are described in order of those more appropriate for avoidance coping styles towards those more appropriate for the approach coping styles. However, randomized trials have not been performed to determine the optimal diversion approach as an adjunct for managing pain in burn patients.

Distraction — Distraction is the most common intervention activated by patients or the provider as an adjunct for pain management in burned children [44]. The types of distraction techniques available to reduce burn pain are limited only by the creativity of patients and health care professionals. Common distraction techniques used with children include bubble blowing, singing songs, reading a story, and counting. Generating distraction strategies for adults may require a bit more creativity, and include engaging in enjoyable conversation during the procedure, listening to music, or
playing a video game [45].

Guided imagery — Imagery is an integrative therapy that incorporates imagined pictures, sounds, or sensations for specific therapeutic goals, such as the reduction of burn pain. While the patient is engaged in the imagery scene, less attention is available for the painful stimuli. It is the patient that selects the imagery. A related discussion on imagery and pain control in cancer patients can be found using the following link. (See "Psychological, rehabilitative, and integrative therapies for cancer pain", section on 'Imagery'.)

Patients using imagery simply create or recreate an image in their mind, presumably one that they find pleasant and engaging. Prior to a painful procedure, we often have the patient elicit a "safe" or “favorite” place to go. This can be a place where they have been before (eg, a favorite vacation spot) or simply a place that they imagine to be relaxing and safe. The clinician then simply cues the patient with the details that they have provided and we encourage them to imagine this place during their subsequent wound care.

Limited evidence suggests that guided imagery is effective in reducing the sensory and emotional components of pain [46]. The Agency for Health Care Policy and Research advocates the use of imagery for reduction of pain intensity and distress for cancer pain and for the management of mild to severe acute pain [47].

Hypnotic analgesia — Hypnosis is an altered state of consciousness characterized by an increased receptivity to suggestion, ability to alter perceptions and sensations, and an increased capacity for dissociation [48]. It is believed that the dramatic shift in consciousness that occurs with hypnosis is the cornerstone of an individual's ability to change their awareness of pain [49]. Hypnotic analgesia should only be used by trained clinicians who can assess the risks and benefits of this powerful technique [48,50].

Although hypnosis involves much more than just avoidance or distraction, the end result is often similar, the patient's focus is diverted from the pain or painful procedure. Several features make hypnotic analgesia a unique method of pain control that differs markedly from imagery or relaxation. Hypnosis may or may not lead to relaxation depending on the nature of the suggestions. In turn, it is not necessary for a patient to be relaxed or even in a deep hypnotic state in order for suggestions to be useful [51]. A related discussion on hypnotic analgesia and pain control in cancer patients can be found using the following link. (See "Psychological, rehabilitative, and integrative therapies for cancer pain", section on 'Hypnotic analgesia'.)

Hypnosis involves several stages, including building clinician-patient rapport, enhancing relaxation through deep breathing, suggestions for deepening the hypnotic state, and narrowing their attention, providing posthypnotic suggestions, and alerting stage [52]. Burn patients are good candidates for hypnotic analgesia because [53-55]:

- The intense nature and severity of burn pain motivates patients to engage in hypnosis.
- The behavioral regression that often occurs after a traumatic injury makes patients more willing to be taken care of by others.
- Patients with burn injuries often experience a dissociative response as a means of coping that may moderate hypnotizability.
- Procedures, which cause the most intense pain, can be scheduled and thus allow hypnosis to be performed in advance of the painful stimulus.

Several studies have shown the positive effect of hypnosis when used in conjunction with prescribed analgesia [55-59]. Patients with higher baseline pain levels have a greater decrease in pain after hypnosis than patients with lower baseline pain levels. However, these studies are limited by methodological differences, lack of uniform assessment of hypnotizability and severity of pain, and small series of burn patients.
Virtual reality — Virtual reality diverts attention away from the painful sensations by immersing patients in a computer generated environment [4,60]. Burn patients can interact with the computer while painful procedures, such as dressing changes, are performed. Observational and small controlled studies indicate that virtual reality is effective in reducing pain and may have utility when used in conjunction with hypnosis [60-65].

Approach technique — The most commonly used approach technique is information provision.

Information provision — Information provision, a technique that actively involves patient input, is an essential element of managing burn pain by providing treatment information in a timely and targeted manner. Information provision assists patient’s understanding of the issues, alternatives, and solutions. This process provides information on how their input will affect the end result, and sharing information can build trust and mutual understanding [66].

Relaxation techniques — Relaxation techniques are used to lower arousal, including unnecessary muscle tension that can increase pain [4,67]. The techniques include deep breathing exercises, progressive muscle relaxation exercises, and cognitive behavioral techniques. There are no randomized trials to determine the optimal relaxation technique to be used as an adjunct for burn pain management.

Deep breathing — Deep breathing, or diaphragmatic breathing, is one of the least time consuming techniques to employ and easiest for adults and children to learn. When a person becomes anxious and/or experiences pain, breathing can become shallow and irregular due to the increased muscle tension in our chest wall. Such shallow breathing, known as thoracic breathing, leads to an increase in muscle tension and subsequent heightened pain [67].

Deep breathing techniques allow patients to become aware of shallow irregular breathing and leads to relaxation that may alleviate some pain. Children can be taught bubble blowing or blowing on a pinwheel to encourage deep breathing. Adults can be taught to place a hand on their stomach and to take a breath deep enough that it passes through their chest and fills their stomach (shallow breathing is more in the chest and will not cause as much hand movement on the stomach). Their hand should rise and fall with the stomach. Exhalation is the most important part of deep breathing exercises and should not be rushed. Diaphragmatic breathing is central to all forms of relaxation and is simple and time efficient.

Progressive muscle relaxation — Muscle tension increases as patients experience stress and pain, hence the focused effort on relaxing and tensing muscles in a controlled manner diverts the attention away from the pain. Progressive muscle relaxation is a technique used to reduce anxiety associated with painful stimuli, such as burn dressing changes, by alternately tensing then relaxing muscles [68]. Muscles are sequentially tensed (10 seconds) and relaxed (20 seconds) through various parts of the body and can be performed during dressing changes. Observational studies suggest that progressive muscle relaxation can decrease recuperation time for hospitalized patients [68]. If a person is unable to actively tense a muscle group due to pain or injury, he or she can still imagine each muscle becoming progressively “warm, heavy, and relaxed” or listen to a tape, a process known as autogenic training [48].

Cognitive behavioral techniques — Cognitive-behavioral therapy (CBT) is used to treat multiple conditions by changing thoughts and behaviors. For treatment of burn patients, CBT includes diversion, information provision, coping skills, and relaxation techniques to modify the patient’s thought process about the painful experience [4]. (See “Overview of psychotherapies”, section on ‘Cognitive and behavioral therapies’.)

Expectations of a bad outcome, such as intense pain, are associated with higher levels of perceived pain [69]. CBT can be used adjunctively to manage these expectations and associated pain in the following manner [70]:

- Recognize that the procedure will cause pain (anticipatory pain or distress).
- Stop the thought that the procedure will cause pain by active efforts to block the thought process.
- Distract from the pain by diverting attention to another thought.
Mindfulness meditation — Mindful meditation is another nonpharmacologic strategy that combines attention, cognitive restructuring, and relaxation. It has gained popularity for its effectiveness for managing acute or chronic pain in adults and adolescents [71,72]. Mindfulness involves purposeful attention on the present moment in a nonjudgmental and accepting manner [73]. Meditation refers to a broad variety of practices that are aimed at clearing the mind to self-regulate the body to achieve a state of relaxation. Several mindfulness meditation practices have been developed to address acute pain [74,75]. Although none have specifically addressed burn pain, its effectiveness in mediating procedural pain for other conditions makes it a promising intervention for acute pain during burn wound care. With the help of a trained professional, mindfulness meditation can be implemented in as little as 20 minutes prior to or during a procedure.

SUMMARY AND RECOMMENDATIONS — The control of burn pain and associated anxiety is a challenge that demands creativity and continued staff training on pain assessment, traditional pharmacologic analgesic approaches, and adjunctive nonpharmacologic techniques. Pharmacologic analgesics should be administered by trained and experienced staff in monitored conditions.

- Pain, which is present at least initially in all burn patients, varies greatly from patient to patient, shows substantial fluctuation over the hospitalization course, and can be unpredictable due to the complex interaction of anatomic, physiologic, psychosocial, and premorbid behavior. (See 'Characteristics of burn pain' above.)

- Pain assessment instruments use visual and/or numeric scales to assess pain intensity, behavioral reactions, and physiologic reactions. There is no one optimal assessment technique for burn patients. The key is to choose an instrument and use it consistently. (See 'Burn pain assessment techniques' above.)

- Pharmacologic agents used to treat burn pain include opioid analgesics, nonopioid analgesics, anxiolytics, and anesthetics. The type of medication used is determined by the severity of pain, the anticipated duration of pain, and intravenous (IV) access. (See 'Pharmacologic treatment options' above.)

- Opioid analgesics (eg, morphine, fentanyl), the most common type of medication used for acute pain relief, are potent and provide a dose dependent degree of sedation important during burn wound care procedures. (See 'Opioid analgesics' above.)

- Nonopioid analgesics (eg, dexmedetomidine, ketamine, NSAIDs), provide short-term effective analgesia and sedation that may be helpful for limited burn debridement and/or dressing changes in adults and children. (See 'Nonopioid analgesics' above.)

- Anxiolytic drugs (eg, benzodiazepines) are useful in premedicating patients for wound care, due to the anticipatory anxiety experienced by these patients prior to and during such procedures. (See 'Anxiolytics' above.)

- Nonpharmacologic treatments should be adjunctive to pharmacologic approaches when treating pain and anxiety in the burn patient. These approaches include cognitive distraction, information provision, relaxation, coping skills, and cognitive behavioral techniques. (See 'Nonpharmacologic treatment options' above.)

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REFERENCES


Burn classification

Graphic 73309 Version 1.0
Adjective Rating Scale for pain assessment

The Adjective Rating Scale allows patients to use descriptive terms to describe the severity of their pain. Scoring can be modified for conversion to a numeric scale.

Original figure modified for this publication. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30:191. Illustration used with the permission of Elsevier Inc. All rights reserved.

Graphic 80858 Version 1.0
The Numeric Pain Scale allows patients to rate the pain on a scale of 0 to 10, with 10 as the worst possible pain.
Visual analog scale

Visual Analog Scale (VAS) (10 cm line).
[Score = 0 to 100 mm] - measuring in millimeters from the left hand end of the line to the point that the patient marks.

Graphic 62346 Version 3.0
### PAINAD - Pain Assessment in Advanced Dementia scale

<table>
<thead>
<tr>
<th>Items*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative vocalization</td>
<td>None</td>
<td>Occasional moan or groan. Low-level speech with a negative or disapproving quality.</td>
<td>Repeated troubled calling out. Loud moaning or groaning. Crying.</td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td>No need to console</td>
<td>Distracted or reassured by voice or touch.</td>
<td>Unable to console, distract or reassure.</td>
<td></td>
</tr>
</tbody>
</table>

This pain assessment score can be used to assess pain in demented patients. Patients should be observed for five minutes prior to performing the assessment. Total scores range from 0 to 10, with 10 representing severe pain.

* Five-item observational tool.

¶ Total scores range from 0 to 10 (based on a scale of 0 to 2 for five items), with a higher score indicating more severe pain (0 = "no pain" to 10 = "severe pain").

*Original figure modified for this publication. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. J Am Med Dir Assoc 2003; 4:9. Illustration used with the permission of Elsevier Inc. All rights reserved.*

Graphic 59509 Version 3.0
## Revised FLACC pain score

<table>
<thead>
<tr>
<th>Categories</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>F Face</td>
<td>0</td>
</tr>
<tr>
<td>No particular expression or smile</td>
<td>Occasional grimace or frown, withdrawn, disinterested; <strong>appears sad or worried</strong></td>
</tr>
<tr>
<td>L Legs</td>
<td>Normal position or relaxed</td>
</tr>
<tr>
<td>A Activity</td>
<td>Lying quietly, normal position, moves easily</td>
</tr>
<tr>
<td>C Cry</td>
<td>No cry (awake or asleep)</td>
</tr>
<tr>
<td>C Consolability</td>
<td>Content, relaxed</td>
</tr>
</tbody>
</table>

This pain score can be used to assess pain from burns and other etiologies for preverbal children.

- Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.
- **Patients who are awake:** Observe for at least 1-2 minutes. Observe legs and body uncovered. Reposition patient or observe activity, assess body for tenseness and tone. Initiate consoling interventions if needed.
- **Patients who are asleep:** Observe for at least 2 minutes or longer. Observe body and legs uncovered. If possible reposition the patient. Touch the body and assess for tenseness and tone.
- The revised FLACC can be used for children with cognitive disability. The additional descriptors (in italics) are included with the original FLACC. The nurse can review the descriptors within each category with parents. Ask them if there are additional behaviors that are better indicators of pain in their child. Add these behaviors to the tool in the appropriate category.

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Graphic 81819 Version 2.0
### Wong-Baker FACES pain rating scale

<table>
<thead>
<tr>
<th>Face</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No hurt</td>
</tr>
<tr>
<td>1</td>
<td>Hurts little bit</td>
</tr>
<tr>
<td>2</td>
<td>Hurts little more</td>
</tr>
<tr>
<td>3</td>
<td>Hurts even more</td>
</tr>
<tr>
<td>4</td>
<td>Hurts whole lot</td>
</tr>
<tr>
<td>5</td>
<td>Hurts worst</td>
</tr>
</tbody>
</table>

Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the child to choose the face that best describes how he is feeling. Rating scale is recommended for persons age three years and older. Point to each face using the words to describe the pain intensity. Ask the child to choose the face that best describes own pain and record the appropriate number.


Graphic 51021 Version 4.0
The OUCHER pain scale uses both pictures and numbers. The pictures can be used for preschool children, while older children can also use the numerical scale. The scales include pictures of Caucasian, African-American, Hispanic, Asian, and First Nation children. The example here depicts a Caucasian child.

The Caucasian version of the Oucher was developed and copyrighted in 1983 by Judith E Beyer, Ph.D., RN, (University of Missouri-Kansas City School of Nursing, Retired), USA. For more information, please visit http://www.oucher.org. Reproduced with permission.
## Intravenous* sedative dosing regimens for managing pain, agitation, and delirium in the intensive care unit

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading dose</th>
<th>Maintenance dose range</th>
<th>Onset (minutes)</th>
<th>Duration of intermittent dose (minutes)</th>
<th>Characteristics and role</th>
</tr>
</thead>
</table>
| **Opioid analgesics**
Fentanyl | 1 to 2 mcg/kg Δ (25 to 100 mcg) ¶ | 0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 35 mcg) ¶ AND/OR 0.7 to 10 mcg/kg/hour infusion (50 to 700 mcg/hour) [1]; For most patients, 1 to 3 mcg/kg/hour infusion (50 to 200 mcg/hour) ¶ with as-needed intermittent bolus doses is sufficient | <1 to 2 | 30 to 60 △ | **Advantages:** Potent analgesic-sedative with immediate onset and less hypotension than other opioid analgesic choices due to relative lack of histamine release. Metabolized heptatically by cytochrome P450-3A4 (CYP3A4) to inactive metabolites. **Disadvantages:** Highly lipophilic parent drug accumulates with repeated or prolonged administration. Chest wall rigidity may occur with higher dosing. **Role:** A good choice for analgesia for most critically ill patients. |
| Hydromorphone | 0.5 to 2 mg Δ | 0.2 to 0.6 mg every one to two hours intermittent AND/OR | 5 to 10 | 240 to 300 | **Advantages:** Requires small volumes relative to other opioids. **Disadvantages:** Requires small volumes relative to other opioids. **Role:** A good choice for analgesia for most critically ill patients. |
0.5 to 3 mg/hour infusion

Disadvantages:
- Potentially neurotoxic (excitatory) metabolite(s) may accumulate in hepatic and/or renal dysfunction.

Role:
- Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.

Disadvantages:
- Can accumulate in hepatic or renal dysfunction.

Advantage:
- CYP metabolism (glucuronidation) may be an advantage for selected patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl.

Role:
- An option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.

Disadvantages:
- Can accumulate in hepatic or renal dysfunction.

Morphine sulfate
- 2 to 10 mg
- 2 to 4 mg every one to two hours intermittent
- 2 to 30 mg/hour infusion
- 5 to 10
- 240 to 300


Page 23 of 59
| Remifentanil ¶ | Optional: 1.5 mcg/kg ¶[1]  
Most ICU patients can be managed without bolus doses; if required, a bolus of 0.5 mcg/kg is usually sufficient; larger boluses are associated with significant reductions in HR | 0.5 to 15 mcg/kg/hour infusion  
Use ideal body weight to determine dose for obese patients ¶ | 1 to 3  
5 to 10 (after cessation of infusion) | Prolonged effects.  
Histamine release and vasoconstriction mediated by venodilation, hypotension, and bradycardia can be significant.  
**Role:** An alternative to fentanyl or hydromorphone where preload reduction and myocardial depressive effects are desirable or tolerable. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment. Avoid in patients with advanced or decompensated liver disease with renal impairment due to risk of accumulation of neurotoxic metabolite.  
**Advantages:** Ultra-short-acting. Cleared by non-specific plasma esterases to inactive metabolites. Does not accumulate in renal or hepatic impairment. Prompt reversal of analgesia and sedation upon discontinuation. |
Disadvantages:
Anticipate pain and discomfort upon abrupt cessation. Glycine excipient may accumulate in renal impairment.

Role:
An alternative to fentanyl for patients requiring frequent neurologic assessments or those with multi-organ failure.

Nonopioid analgesics (adjunctive or opioid sparing)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>Oral, rectal: 325 to 1000 mg every four to six hours. IV: 650 mg IV every four hours to 1000 mg IV every six hours, or 15 mg/kg IV every six hours for patients weighing &lt;50 kg. Maximum ≤4 g/day.</td>
<td>Lacks dependence and tolerance of opioids. Lacks antiplatelet effect and gastrointestinal toxicity of NSAIDs.</td>
<td>Lacks significant anti-inflammatory effect. IV preparation requires administration over 15 minutes. Can cause hepatotoxicity in chronic or acute overdosage. Avoid or use a lower daily dose in older adults and patients at risk for hepatoxicity (eg, heavy alcohol use or malnourished). Interacts with warfarin.</td>
</tr>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>Oral: 30 to 60. Rectal: Variable. IV: 5 to 10. 240 to 360.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Ketorolac</strong></td>
<td><strong>Optional:</strong> 30 mg once</td>
<td><strong>Age &lt;65 years and weight ≥50 kg:</strong> 15 to 30 mg every six hours; maximum 120 mg/day for up to five days</td>
<td><strong>IV:</strong> ~30</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

**Advantages:**
- Lacks dependence and tolerance of opioids.
- Effective anti-inflammatory.

**Disadvantages:**
- Can cause or worsen renal insufficiency.
- Dose-related risk of gastropathy.
- Reversibly inhibits platelet functioning.
- May alter cardioprotective effect of aspirin.

**Role:**
- Adjunctive analgesic that may reduce opioid requirements.
- Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, and ischemic heart disease.
<table>
<thead>
<tr>
<th>Drug</th>
<th>None</th>
<th>Oral: 400 mg orally every four hours (maximum 2.4 g/day chronic)</th>
<th>Oral: 30 IV: ~30</th>
<th>240 to 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>None</td>
<td>IV: 400 to 800 mg IV every six hours (maximum 3.2 g/day acute)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Advantages:**
- Lacks dependence and tolerance of opioids.
- Effective anti-inflammatory.

**Disadvantages:**
- Can cause or worsen renal insufficiency.
- Dose-related risk of gastropathy.
- Reversibly inhibits platelet functioning.
- Can alter cardioprotective effect of aspirin.

**Role:**
- Short-term treatment of moderate acute pain and febrile conditions.
- Adjunctive analgesic that may reduce opioid requirements.
- Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, ischemic heart disease, heart failure, reduced cardiac output, hypovolemic state, asthma, or cirrhosis.
- Contraindicated in treatment of perioperative pain in coronary artery bypass graft surgery. Patients should be well hydrated.
| **Gabapentin** | **None** | **Oral: Initially 100 mg three times per day**<br>**Oral: Maintenance 900 to 3600 mg per day in three divided doses** | **Variable** | **--** |

**Advantages:**
- Effective for treatment of neuropathic pain.
- Low risk of drug interactions.

**Disadvantages:**
- Requires enteral administration, scheduled dosing, and individualized titration over days to weeks.
- Oral bioavailability is variable (27 to 60%) and inversely proportional to dose.
- Adverse effects include sedation, dizziness, and ataxia, which may be intensified in renal impairment, requiring dose adjustment.
- Should not be abruptly stopped due to risk of discontinuation symptoms.

**Role:**
Useful adjunct to other analgesic...
| Medication | None | Oral: Initially 75 mg once or twice per day<br>Oral: Maintenance 150 to 300 mg twice per day | Variable (hours to days) | -- |

**Advantages:**
- Effective for the treatment of neuropathic pain
- Oral bioavailability (>90%) is more reliable than gabapentin and may provide for more rapid onset of analgesia with a shorter amount of time needed to titrate to full dose.
- Low risk of drug interactions.

**Disadvantages:**
- Requires enteral administration, scheduled dosing, and titration over days to weeks.
- Adverse effects include sedation, dizziness, and ataxia, which may be intensified in renal impairment, requiring dose adjustment. Should not be abruptly stopped due to risk of discontinuation symptoms.

**Role:**
Useful adjunct to other treatments for neuropathic pain.
<table>
<thead>
<tr>
<th><strong>Anesthetic-sedative</strong></th>
<th><strong>Propofol</strong></th>
<th><strong>Initial rate 5 mcg/kg/minute</strong></th>
<th><strong>5 to 50 mcg/kg/minute</strong></th>
<th><strong>&lt;1 to 2</strong></th>
<th><strong>3 to 10</strong></th>
<th><strong>Advantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Titrates every 5 to 10 minutes in increments of 5 to 10 mcg/kg/minute. Some patients require up to 70 mcg/kg/minute, which can increase risk of propofol infusion syndrome (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dosage regimens, and adverse effects).</td>
<td></td>
<td></td>
<td></td>
<td>Potent sedative-hypnotic associated with an immediate onset and rapid awakening upon discontinuation when administered for short-term use. Metabolism is reportedly unaltered in hepatic or renal impairment and subject to few significant drug interactions. Infusion is readily titratable to desired depth of sedation, minimizing risk of oversedation. Propofol effectively decreases intracranial pressure, cerebral metabolism, controls intractable seizures, and may reduce shivering in the rewarming phase of induced hypothermia following...</td>
</tr>
</tbody>
</table>
Disadvantages: Adverse effects include hypotension, bradycardia, respiratory depression, decreased myocardial contractility, elevated triglycerides, peripheral injection site pain, rarely propofol infusion syndrome (refer to UpToDate topics on analgesic medications in critically ill patients: properties, dosage regimens, adverse effects). Specific product presentations may include potential allergens (egg, soy, peanut, others). Consult product label information.

No analgesic effects.

Role: A good choice in conjunction with appropriate analgesia for short-term sedation of patients in whom rapid awakening is advantageous. Also a good choice to decrease elevated resuscitation from cardiac arrest.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Infusion Rate</th>
<th>Maximum HR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>0.1 to 0.5 mg/kg</td>
<td>0.05 to 0.4 mg/kg/hour</td>
<td>≤1</td>
<td>10 to 15 (single dose)</td>
</tr>
</tbody>
</table>

**Advantages:**
- Potent dissociative sedative-anesthetic with marked analgesia that maintains cardiac output and mean arterial pressure without inhibition of respiratory drive.
- Does not inhibit protective reflexes.
- May reduce acute opioid tolerance.

**Disadvantages:**
- Sympathetic stimulation (ie, increased heart rate and myocardial oxygen demand, elevated intracranial pressure and systemic blood pressure) may be intolerable depending upon clinical setting.
- Rarely, cardiorespiratory depression associated with rapid administration or higher doses.
- Adverse effects may include...
Hallucinations, delirium upon withdrawal, tonic-clonic movements, dissociative experiences, unpleasant recall, hypersalivation, nausea, and vomiting. Complex metabolism includes CYP3A4, 2C9, 2B6, and non-CYP hepatic transformations and an active metabolite (norketamine), which may accumulate in renal and/or hepatic impairment or due to drug interactions.

**Role:** An alternate choice for postsurgical pain management, severe agitation, or as an adjunctive analgesic in patients with severe refractory pain in clinical settings where increased myocardial oxygen demand and sympathetic tone are tolerable.

**Central alpha₂ agonist**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Optional:</th>
<th>0.2 to 0.7 mcg/kg/hour</th>
<th>5 to 10 (optional loading dose)</th>
<th>60 to 120</th>
<th><strong>Advantages:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine</td>
<td>1 mcg/kg over 10 minutes if hemodynamically stable</td>
<td>Initiate at 0.2 mcg/kg/hour and titrate every 30</td>
<td>15 (without loading dose)</td>
<td>Effective sympatholytic (central alpha agonist)</td>
<td></td>
</tr>
</tbody>
</table>
Usually not given minutes
Some patients require doses up to 1.5 mcg/kg/hour

---

Moderate and analgesic effect. No clinically significant respiratory depression. Character and depth of sedation may permit critically ill, mechanically ventilated patients to be interactive or easily awakened, yet comfortable. Can be used in non-mechanically ventilated ICU patients and continued as needed following extubation.

Reduces shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. May be less likely to cause delirium than other sedative choices.

**Disadvantages:**
Potential significant hypotension, bradycardia, and hypertension do not resolve quickly upon abrupt discontinuation. Metabolized hepatically by glucuronidation and CYP2A6. Dose reduction recommended with...
renal and hepatic impairment. Loading dose may be associated with cardiovascular instability, tachycardia, bradycardia, heart-block. Does not induce the deep sedation needed for neuromuscular blockade.

**Role:** A good choice for short- and long-term sedation in critically ill patients without relevant cardiac conditions. May be useful for sedation of patients with or at high risk of developing delirium, although this has not been well established.

### Benzodiazepines

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dose</th>
<th>Infusion Rate</th>
<th>Duration</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>0.01 to 0.05 mg/kg&lt;sup&gt;Δ&lt;/sup&gt; (0.5 to 4 mg)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>0.02 to 0.1 mg/kg/hour infusion (2 to 8 mg/hour)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>2 to 5</td>
<td>potent amnestic and anxiolytic agent with an immediate onset of action and a short duration of effect when administered short-term (&lt;48 hours). It is the only IV benzodiazepine that is not delivered in propylene glycol.</td>
<td></td>
</tr>
</tbody>
</table>
Hepatically metabolized by CYP3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long-term. Half-life may be prolonged in critically ill patients with hepatic or renal impairment.

Risk of delirium. Also, it interacts with drugs used in the ICU (eg, some antiretrovirals,azole antifungals) that alter CYP metabolism such that excess sedation can occur with concomitant use of midazolam and drugs metabolized by CYP3A4.

**Role:** A good choice for short-term anxiolysis and treatment of acute agitation. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment.

<table>
<thead>
<tr>
<th>Lorazepam</th>
<th>0.02 to 0.04 mg/kg $^\Delta$ (1 to 2 mg) $^\dagger$</th>
<th>0.02 to 0.06 mg/kg every two to four hours intermittent (1 to 4 mg) $^\dagger$</th>
<th>15 to 20</th>
<th>360 to 480 $^\circ$</th>
</tr>
</thead>
</table>

**Advantages:** Sedative, amnestic, potent anxiolysis with anticonvulsant properties.

$^\Delta$ Hepatic

$^\dagger$ Delta

$^\circ$ Circle

(0.5 to 10 mg/hour)

metabolized by glucuronidation to inactive metabolites. Relatively low risk of drug interactions and safety in mild to moderate hepatic and renal impairment.

Disadvantages: Relatively slow onset. Risk of sedation when titrating dose due to delayed response and accumulation in peripheral tissues. Risk of delirium. Incompatibilities and risk of line precipitate. Propylene glycol solvent may accumulate with prolonged use or high dosing causing metabolic acidosis and end-organ dysfunction (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dosage regimens, and adverse effects).

Role: A good choice for sedation and anxiolysis for most patients, including those who may require long-term ongoing...
sedation. Intermittent dosing may be preferred, but continuous infusion may be initiated for patients requiring frequently repeated higher dosing.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (mg/kg) Intermittent</th>
<th>Dose (mg/kg) Continuous Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.05 to 0.2 mg/kg (5 to 10 mg)</td>
<td>0.03 to 0.1 mg/kg every 0.5 to 6 hours (1 to 7 mg)</td>
</tr>
</tbody>
</table>

Continuous infusion is not recommended.

Advantages:
- Rapid onset with potent sedative and muscle-relaxant effects.

Disadvantages:
- Hepatically metabolized by CYP2C19 and 3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long-term. Half-life may be prolonged in critically ill patients with hepatic and/or renal impairment.
- Risk of delirium.
- Also, it interacts with drugs used in the ICU that alter CYP metabolism.

Injection solution contains propylene glycol solvent and cannot be delivered as a continuous infusion. Injection site pain and risk of phlebitis limit usefulness of IV injections.

Role: Seldom used for sedation.
Critically ill patients may be at risk of withdrawal seizures due to drug overdose or poisoning. Antipsychotics may be useful for critically ill patients at risk of alcohol withdrawal or seizures due to drug overdose or poisoning.

### Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.03 to 0.15 mg/kg</td>
</tr>
</tbody>
</table>

Variable doses; refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dosage regimens, and adverse effects.

Moderate sedating dopamine antagonist for control of positive symptoms of delirium and ICU psychoses. Minimal cardiorespiratory effects in euvolemic, hemodynamically stable patients.

Disadvantages include complex hepatic metabolism that includes CYP3A4 and 2D6 transformations. Some experts consider certain metabolites to be active or potentially neurotoxic. Half-life becomes prolonged with repeated administration.

Adverse effects include dose-dependent QT interval prolongation and hypotension. Interacts with some common ICU drugs by interference with

<p>| | | | | | | | |</p>
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</tbody>
</table>

| Olanzapine † | Optional: 5 to 10 mg IM | Oral: Initially 5 to 10 mg once daily; increase every 24 hours as needed by 5-mg increments up to 20 mg/day | IM: 15 to 45 | IM: ≥120 |

**Role:** Potential treatment for agitation and/or delirium in critically ill patients.

**Advantages:**
- Availability of short-acting IM formulation; less risk of extrapyramidal symptoms and QT prolongation than haloperidol.

**Disadvantages:**
- Adverse effects include orthostatic hypotension, hyperglycemia, somnolence, QT interval prolongation, and anticholinergic effects. Undergoes extensive hepatic metabolism including non CYP (ie, glucronidation) and CYP1A2 transformations. Half-life may be prolonged (ie, ≥50 hours) with increased risk of accumulation in patients who are metabolised by having an additive effect, prolonging the QTc.

**Extrapyramidal symptoms and neuroleptic malignant syndrome** are rare in critical care use.
Role: Potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation and/or delirium in the ICU. Use lowest starting dose and titrate more gradually in patients with renal and/or hepatic impairment and/or other factors that predispose for slowed metabolism (see 'Disadvantages' above).

| Quetiapine‡ | None | Oral: Initially 50 mg every 12 hours; increase every 24 hours as needed up to 400 mg/day | Oral: 60 (initial effect); ≥24 hours (full effect) | Oral: 6 to 12 hours |

Advantages: risk of extrapyramidal symptoms and possibly less risk of QT prolongation than haloperidol.

Disadvantages: Requires enteral route of administration and scheduled dosing due to slow onset of action and relatively gradual titration schedule. Adverse effects may include sedation or orthostatic hypotension.
### Ziprasidone†

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optional:</td>
<td>10 mg IM May repeat every two hours if needed (maximum 40 mg total) OR 20 mg IM May repeat once after four hours if needed (maximum 40 mg total)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>10 to 40 mg orally every 12 hours</td>
<td>IM: 30</td>
</tr>
<tr>
<td>IM: 30</td>
<td></td>
<td>IM: ≥90</td>
</tr>
</tbody>
</table>

**Role:** A potential choice as as-needed haloperidol alternative for treatment of agitation and/or delirium. In advanced hepatic impairment, initiate with reduced dose and titrate in lower increments.

**Advantages:** Availability of short-acting IM formulation; less risk of extrapyramidal symptoms than haloperidol.

**Disadvantages:** Orthostatic hypotension, hyperglycemia, QT interval prolongation; undergoes extensive hepatic metabolism by hepatic non CYP and CYP3A4 transformations to active and inactive metabolites; IM formulation contains cyclodextrin (a potential nephrotoxin).
can accrue renal impairment; an IV formulation is not available.

**Role:** A potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation in the ICU. Dose reduction is needed in advanced hepatic impairment. Specific recommendations are not available. Avoid prolonged use of IM preparation in patients with renal impairment due to risk of accumulation of cyclodextrin additive.

Data provided on drug metabolism and presence of active metabolite(s) are included to assess the potential for drug interactions and risk of drug accumulation in renal and/or hepatic impairment.

CYP: cytochrome P-450 metabolism; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatories; INR: international normalized ratio; IM: intramuscularly; QT: QT interval on the electrocardiogram; QTc: corrected QT interval; ICU: intensive care unit.

* All doses shown are for IV administration except where otherwise noted (eg, oral or rectal acetaminophen, IM olanzapine optional initial dose).

¶ In patients who are **obese**, standard, non-weight-based initial dosing is preferred. Standard adult doses, ie, scaled to ideal body weight, are shown in parentheses following weight-based doses. A separate calculator to determine ideal body weight is available in UpToDate. For additional information refer to UpToDate topic review on intensive care unit management of the complicated postoperative bariatric surgery patient.

Δ One or more loading doses may be needed. See onset of action data for minimum time between re-dosing. Loading dose should be reduced or omitted in patients that are older, hypovolemic, having increasing vasopressor requirements, or at-risk for hemodynamic compromise.

◊ Duration of action shown is for initial dosing. Duration becomes significantly prolonged after repeated dosing or with administration as a continuous infusion due to accumulation of drug in adipose tissue.

§ As with all opioids, tolerance may require dose escalation, and withdrawal syndrome may be precipitated upon abrupt discontinuation.
Dosing of haloperidol in agitated schizophrenia differs from the recommendations listed in this table for delirium in the ICU and is reviewed separately. Refer to topic reviews of emergency management of the acutely agitated or violent patient and pharmacotherapy for acute schizophrenia.

† The precise role of second-generation antipsychotics in the treatment or prevention of delirium in ICU is not established. Quetiapine and olanzapine recommendations and data are based on limited experience and small trial results (Devlin et al. Crit Care Med 2010; 38:419; Skrobik et al. Intensive Care Med 2004; 30:444).


Data from:
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# Opioid Analgesics for Use in Children with Burns

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic Dose*</th>
<th>Oral Dose and Frequency ¶</th>
<th>IV Dose and Frequency ¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral (mg)</td>
<td>IV (mg)</td>
<td></td>
</tr>
<tr>
<td>MorphineΔ</td>
<td>30</td>
<td>10</td>
<td>0.3 mg/kg every three to four hours</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td>0.04 to 0.08 mg/kg every three to four hours</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>N/A</td>
<td>0.1 to 0.2 mg/kg every three to four hours</td>
</tr>
<tr>
<td>Fentanyl◊</td>
<td>N/A</td>
<td>0.1 (100 mcg)</td>
<td>N/A</td>
</tr>
<tr>
<td>Methadone</td>
<td>§</td>
<td>§</td>
<td>0.1 mg/kg every eight to twelve hours</td>
</tr>
</tbody>
</table>

N/A: not available.

* Approximate equianalgesic dose for estimation when changing opioid agents.

¶ Doses are for individuals over 6 months of age with a maximum weight of 50 kg. Oral doses refer to immediate release products.

Δ Dose adjustment for renal insufficiency may be required. Not recommended in severe renal insufficiency.

◊ Oral transmucosal fentanyl is commonly used in pediatric burn patients for procedural pain, due to its acceptance by children, its relatively fast onset of action, and its relatively short duration of action, at a dose of 10-20 mcg/kg.

§ Due to gradual drug accumulation at tissue sites, the dose and frequency of methadone differ for initial compared with repeated use; dose and interval given is usual after repeated use; methadone should be initiated and titrated by a clinician experienced with its use.


Graphic 76614 Version 5.0
**Patient controlled analgesia (PCA) regimens for opioid naïve adult patients: commonly-prescribed dose ranges**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>Initial loading and rescue loading dose range</th>
<th>Demand (PCA) dose range</th>
<th>Lockout interval</th>
<th>Maximum in four hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 mg/mL</td>
<td>0.5 to 2.5 mg*</td>
<td>0.5 to 2.5 mg</td>
<td>5 to 10 minutes</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg/mL</td>
<td>0.05 to 0.4 mg¶</td>
<td>0.05 to 0.4 mg</td>
<td>5 to 10 minutes</td>
<td>6 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10 mcg/mL</td>
<td>5 to 20 mcgΔ</td>
<td>5 to 20 mcg</td>
<td>4 to 10 minutes</td>
<td>300 mcg</td>
</tr>
</tbody>
</table>

- Dosing should be individualized according to patient-specific factors, clinical situation, comorbidities, and concurrent medications. Lower doses and closer monitoring including continuous pulse oximetry and end-tidal carbon dioxide are recommended during the early post-operative period, in older adults, and in patients at elevated risk for respiratory depression, hypoxia, and/or opioid accumulation, eg, due to obstructive airway disease, sleep apnea, obesity, low body weight, frailty, renal and/or hepatic impairment, or use with other medications with sedating and/or respiratory depressant properties.
- Adjunctive medications for management of opioid-associated pruritus and nausea may be needed (eg, diphenhydramine, prochlorperazine). Refer to "Management of acute perioperative pain" topic for detail.
- The use of a continuous infusion (basal opioid infusion) is not recommended; such use should be limited to carefully selected patients who are opioid tolerant and/or receiving care in a critical care unit.
- PCA dose ranges and other detail shown in the table are based upon recommendations used at experienced centers; protocols will vary by institution. For additional detail, refer to the individual drug monographs provided by Lexicomp included with UpToDate.

PCA: Patient-controlled analgesia.

* Morphine initial loading dose may be given incrementally in smaller divided doses every six minutes as needed. A single loading dose should not exceed 2.5 mg and total loading dose should not exceed 10 mg. A rescue loading dose may be repeated after eight hours if needed.
¶ Hydromorphone initial loading dose may be given incrementally in smaller divided doses every six minutes as needed. A single dose should not exceed 0.4 mg and total loading dose should not exceed 2 mg. A rescue loading dose may be repeated after eight hours if needed.
Δ Fentanyl initial loading dose may be given incrementally in smaller divided doses every six minutes as needed. A single loading dose should not exceed 20 mcg and total loading dose should not exceed 100 mcg.
mcg. A rescue loading dose may be repeated after eight hours if needed.

Graphic 101248 Version 4.0
### Orally available nonopioid analgesic and nonsteroidal antiinflammatory drugs (NSAIDs): Usual dosing for adults with pain or inflammation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Optional initial loading dose</th>
<th>Usual analgesic dose (oral)</th>
<th>Maximum dose per day (mg)</th>
<th>Selected characteristics and role in therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Para-aminophenol derivative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen* (paracetamol, APAP)</td>
<td>None</td>
<td>325 to 650 mg every 4 to 6 hours, or 1000 mg every 6 hours up to three times per day</td>
<td>3000 mg</td>
<td>- Effective for noninflammatory pain; may be opioid-sparing.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Doses &lt;2000 mg per day do not increase risk of serious GI complications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Does not alter platelet functioning.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Can cause hepatotoxicity in chronic or acute overdosage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Avoid or use a lower total daily dose (maximum 2000 mg per day) in older adults, patients at risk for hepatotoxicity (eg, regular alcohol use, malnourished) or with organ dysfunction.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- For short-term or one-time use, may use a total dose of up to 4000 mg per day in selected medically supervised patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Interacts with warfarin (prolongs INR), isoniazid, and CYP450-inducing drugs (transaminitis).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Warn patients about acetaminophen content in combination prescription (eg, oxycodone-acetaminophen) and OTC preparations.</td>
</tr>
</tbody>
</table>

**NSAID agents**
Applies to all nonselective NSAIDs:

- Effective for treatment of acute and chronic painful and inflammatory conditions. May decrease opioid requirements. Short- to moderate acting NSAIDs (eg, naproxen, ibuprofen) are preferred for most patients.
- Dose- and age-related risk of gastropathy.
- May cause or worsen renal impairment.
- Nonselective NSAIDs reversibly inhibit platelet functioning and can alter cardioprotective effects of aspirin.
- Avoid NSAIDs in patients with renal insufficiency (CrCl <60 mL/minute), GI bleeding, platelet dysfunction, reduced cardiac output, difficult to control hypertension, hypovolemia, hyponatremia, aspirin-sensitive asthma, or cirrhosis.
- Safety concerns of NSAID use in patients with or at elevated risk for cardiovascular disease or thrombotic events are addressed in a separate topic review in UpToDate.
- Use with caution or avoid in patients receiving co-medication with anticoagulants, systemic glucocorticoids, lithium, loop diuretics, and other interacting drugs. Drug interactions may be checked using the Lexi-Interact program included with UpToDate.
- Though some older adults may benefit from a brief course of NSAID at lowest effective dose, use in most older adults should be avoided. Refer to UpToDate separate topic reviews of treatment of pain in older adults and with organ dysfunction.

**Salicylate (acetylated)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Frequency (every)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin*</td>
<td>2600</td>
<td>4 to 6 hours</td>
<td>4000</td>
</tr>
</tbody>
</table>

- Standard for comparison, but now used infrequently for treatment of chronic pain and inflammation.
- Unlike other NSAIDs, irreversibly inhibits platelet functioning for life of the platelet (7 to 10 days).

**Salicylates (nonacetylated)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Frequency (every)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diflunisal</td>
<td>1000</td>
<td>8 to 12 hours</td>
<td>1500</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate</td>
<td>1500</td>
<td>8 to 12 hours</td>
<td>3000</td>
</tr>
<tr>
<td>Salsalate</td>
<td>1500</td>
<td>8 to 12 hours</td>
<td>3000</td>
</tr>
</tbody>
</table>

- Applies to all nonacetylated salicylates:
  - No significant effect on platelet function at usual analgesic doses.
  - Less frequently associated with GI bleeding than nonselective NSAIDs at usual analgesic doses.
  - Generally tolerated by adults with asthma at lower daily doses: Diflunisal ≤1000 mg, choline magnesium...
trisalicylate and salsalate \( \leq 2000 \text{ mg} \).
- Relatively slow onset.
- 500 mg dose of diflunisal has a comparable analgesic effect with 650 mg acetaminophen or aspirin.

### Propionic acids (phenyl-propionic acid)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Total Daily Dose</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **Naproxen**      | 500 mg (naproxen base) | 250 to 500 mg every 12 hours (naproxen base) | 1250 mg acute, 1000 mg chronic (naproxen base) | A good choice for treatment of acute or chronic pain and inflammation in most patients if NSAID therapy is indicated. High doses (eg, 500 mg twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs.◊
<p>|                   | 550 mg (naproxen sodium) | 275 to 550 mg every 12 hours (naproxen sodium) | 1375 mg acute, 1100 mg chronic (naproxen sodium) | For the treatment of rheumatologic disorders, total daily dose may be increased to a maximum of 1500 mg base (1650 mg naproxen sodium) when needed. Naproxen sodium has more rapid absorption and onset of effect than naproxen base. |
| <strong>Ibuprofen</strong>     | 1600 mg | 400 mg every 4 to 6 hours | 3200 mg (acute), 2400 mg (chronic) | 200 to 400 mg dose has a comparable analgesic effect with 650 mg acetaminophen or aspirin. Short duration of effect. Useful alternative to naproxen in patients without cardiovascular risks. |
| <strong>Ketoprofen</strong>    | 100 mg | 50 mg every 6 hours or 75 mg every 8 hours | 300 mg | 25 mg dose has a comparable analgesic effect to 400 mg ibuprofen. Short duration of effect. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dosage Schedule</th>
<th>Maximum Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flurbiprofen</td>
<td>100 mg</td>
<td>50 to 100 mg every 6 to 12 hours</td>
<td>300 mg</td>
<td>Lozenge preparation available in some countries.</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>None</td>
<td>1200 mg once daily</td>
<td>26 mg/kg up to 1800 mg (whichever is lower)</td>
<td>Long duration of effect.</td>
</tr>
<tr>
<td><strong>Acetic acids (pyrano-indoleacetic acid)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75 or 100 mg (conventional tablets)</td>
<td>50 mg every 8 hours</td>
<td>150 mg</td>
<td>Diclofenac is also available as a topical patch, solution, and gel for treatment of musculoskeletal pain and osteoarthritis of superficial joints, which may be useful in combination with or as an alternative to systemic NSAIDs. Refer to UpToDate review of initial treatment of osteoarthritis and separate table. Interacts with drugs that are strong inhibitors or inducers of CYP2C9 drug metabolism; use Lexi-Interact to determine specific interactions.</td>
</tr>
<tr>
<td>Etodolac</td>
<td>400 to 600 mg</td>
<td>Immediate release: 200 to 400 mg every 6 to 8 hours Extended release: 400 to 1000 mg once daily</td>
<td>Immediate release: 1000 mg Extended release: 1200 mg</td>
<td>Relatively COX-2 selective at lower total daily dose of 600 to 800 mg. 200 mg dose has a comparable analgesic effect with 400 mg of ibuprofen.</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>75 mg</td>
<td>Immediate release: 25 to 50 mg every 8 to 12 hours Controlled release: 75 mg once or</td>
<td>150 mg</td>
<td>Useful for treatment of acute gout and specific types of headache. Potent inhibitory effects on renal prostaglandin synthesis. More frequently associated with CNS side effects (eg,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Administration</th>
<th>Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolmetin</td>
<td>600 mg</td>
<td>400 to 600 mg every 8 hours</td>
<td>1800 mg</td>
<td>Carefully select and monitor patients to reduce risk of renal and cardiovascular toxicities.</td>
</tr>
<tr>
<td>Sulindac</td>
<td>300 mg</td>
<td>150 to 200 mg every 12 hours</td>
<td>400 mg</td>
<td>More frequently associated with hepatic inflammation (idiosyncratic or with features of hypersensitivity) compared with other NSAIDs. Sulindac metabolites implicated in the formation of renal calculi; refer to topic review of nonselective NSAID adverse effects. Prescribing should be limited to specialists with experience in treatment of chronic pain and inflammation.</td>
</tr>
<tr>
<td>Oxicams (enolic acids)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5 mg (conventional tablets)</td>
<td>7.5 to 15 mg once daily</td>
<td>15 mg</td>
<td>Long duration of effect; slow onset. Relatively COX-2 selective and minimal effect on platelet function at lower total daily dose of 7.5 mg. Rarely associated with serious cutaneous allergic reactions, including Stevens-Johnson syndrome.</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>10 mg</td>
<td>10 to 20 mg once daily</td>
<td>20 mg</td>
<td>A long-acting option for treatment of chronic pain and inflammation poorly responsive to other NSAIDs. Daily doses ≥20 mg increase risk of serious GI</td>
</tr>
</tbody>
</table>
complications.
- Concurrent pharmacologic gastroprotection is suggested.
- Rarely associated with serious cutaneous allergic reactions, including Stevens-Johnson syndrome.
- Prescribing should be limited to specialists with experience in treatment of chronic pain and inflammation.

**Fenamates (anthranilic acids)**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose</th>
<th>Dosage</th>
<th>Maximum Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meclofenamate (meclofenamic acid)</td>
<td>150 mg</td>
<td>50 mg every 4 to 6 hours</td>
<td>400 mg</td>
<td>Alternate NSAID choice for treatment of acute or chronic pain, inflammation, and dysmenorrhea. Appears to be associated with higher incidence of GI disturbance (including diarrhea) compared with other nonselective NSAIDs.</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>500 mg</td>
<td>250 mg every 6 hours</td>
<td>1000 mg</td>
<td>Alternate NSAID choice for treatment of acute pain and dysmenorrhea. Duration of use not to exceed seven days (acute pain) or three days (dysmenorrhea). Antiinflammatory efficacy is comparatively low. Not indicated for treatment of chronic pain or inflammation.</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1000 mg</td>
<td>500 to 750 mg every 8 to 12 hours or 1000 to 1500 mg once daily</td>
<td>2000 mg</td>
<td>Moderate duration of effect; slow onset. Relatively COX-2 selective at lower total daily dose of 1000 mg or less. Minimal effect on platelet</td>
</tr>
</tbody>
</table>
### Selective COX-2 inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Dose</th>
<th>Administration</th>
<th>Total Daily Dose</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Celecoxib                        | 400 mg | 200 mg daily or 100 mg every 12 hours | 400 mg          | - Relative reduction in GI toxicity compared with nonselective NSAIDs.  
                                |      |                                  |                  | - No effect on platelet function.                                      
                                |      |                                  |                  | - Cardiovascular and renal risks are dose-related and appear similar to those of nonselective NSAIDs. |
|                                  |      |                                  |                  | - Patients with indications for cardioprotection require aspirin supplement; individuals may require concurrent gastroprotection. |
| Etoricoxib (not available in United States) | None | 30 to 60 mg once daily            | 60 mg (chronic pain and inflammation) 120 mg (acute pain for up to eight days) | - May be associated with more frequent and severe dose-related cardiovascular effects (eg, hypertension) compared with nonselective and other COX-2 selective NSAIDs.  
                                |      |                                  |                  | - Otherwise, risks and benefits as with celecoxib (see above).         |

GI: gastrointestinal; INR: international normalized ratio; CNS: central nervous system; CYP450: cytochrome P450; OTC: over the counter, available without prescription; CrCl: creatinine clearance; COX-2: cyclooxygenase isoform 2; NSAID: nonsteroidal antiinflammatory drug; SSRIs: selective serotonin reuptake inhibitors.

* Available without a prescription in the United States.
¶ A list of CYP450-inducing drugs is available separately in UpToDate.
∆ NSAIDs may interact with aspirin, warfarin, methotrexate, antihypertensives, serotonin reuptake inhibitor antidepressants (eg, SSRIs, cyclic antidepressants, venlafaxine), and other drugs. For specific interactions, use the Lexi-Interact program included with UpToDate.
◊ Refer to the UpToDate topic on the cardiovascular effects of nonselective NSAIDs.
§ For additional information on gastroprotective strategies, including selective COX-2 inhibitors and other options, refer to the UpToDate topics on the overview of selective COX-2 inhibitors and on NSAIDs (including aspirin) and the primary prevention of gastroduodenal toxicity.

Prepared with data from:


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### Pharmacology of benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult oral total daily dose (mg)*</th>
<th>Comparative potency (mg) ¶</th>
<th>Onset after oral dose (hours)</th>
<th>Metabolism</th>
<th>Elimination half-life (hours) Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Used primarily to treat anxiety symptoms/anxiety disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5 to 6</td>
<td>0.5</td>
<td>1</td>
<td>CYP3A4 to minimally active metabolites.</td>
<td>11 to 15</td>
</tr>
<tr>
<td>Alprazolam extended release</td>
<td>0.5 to 6, once daily</td>
<td>0.5</td>
<td>1</td>
<td></td>
<td>16 (older adults) 20 (hepatic impairment) 22 (obesity)</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>6 to 30</td>
<td>7.5</td>
<td>1</td>
<td>CYP1A2. No active metabolite.</td>
<td>8 to 20</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>5 to 100</td>
<td>10</td>
<td>1</td>
<td>CYP3A4 to active metabolites.</td>
<td>30 to 100</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 to 4</td>
<td>0.25 to 0.5</td>
<td>0.5 to 1</td>
<td>CYP3A4. No active metabolite.</td>
<td>18 to 50</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>15 to 60</td>
<td>7.5</td>
<td>0.5 to 1</td>
<td>CYP3A4 to active metabolite.</td>
<td>36 to 200</td>
</tr>
<tr>
<td>Diazepam</td>
<td>4 to 40</td>
<td>5</td>
<td>0.25 to 0.5</td>
<td>CYP2C19 and 3A4 to active metabolites.</td>
<td>50 to 100</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 to 6</td>
<td>1</td>
<td>0.5 to 1</td>
<td>Non-CYP glucuronidation in liver. No active metabolite.</td>
<td>10 to 14</td>
</tr>
<tr>
<td></td>
<td>0.5 to 4 (hypnotic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30 to 120, 15 to 30</td>
<td>15 to 30</td>
<td>1 to 2</td>
<td>Non-CYP glucuronidation</td>
<td>5 to 15</td>
</tr>
</tbody>
</table>
### Used primarily to treat insomnia

<table>
<thead>
<tr>
<th>Drug</th>
<th>(hypnotic)</th>
<th>Half-life (h)</th>
<th>CYP and Non-CYP Metabolism</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazepam 15 to 60</td>
<td>15</td>
<td>2 to 3</td>
<td>CYP3A4 to active metabolites.</td>
<td>30 to 200 Prolonged in older adults</td>
</tr>
<tr>
<td>Estazolam 1 to 2</td>
<td>0.3</td>
<td>0.5 to 1</td>
<td>CYP3A4 to minimally active metabolite.</td>
<td>10 to 24</td>
</tr>
<tr>
<td>Flurazepam 15 to 30</td>
<td>5</td>
<td>0.5 to 1</td>
<td>CYP3A4 to active metabolites.</td>
<td>40 to 114 120 to 160 (older adults)</td>
</tr>
<tr>
<td>Nitrazepam 5 to 10</td>
<td>5</td>
<td>0.5 to 1</td>
<td>Non-CYP acetylation in liver. No active metabolites.</td>
<td>24 to 30 40 (older adults)</td>
</tr>
<tr>
<td>Temazepam 7.5 to 30</td>
<td>5</td>
<td>0.5 to 1</td>
<td>Primarily non-CYP glucuronidation in liver to minimally active metabolite.</td>
<td>8 to 15</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 to 0.25</td>
<td>0.25 to 0.5</td>
<td>CYP3A4. No active metabolite.</td>
<td>2 to 5</td>
</tr>
<tr>
<td>Quazepam 7.5 to 15</td>
<td>5</td>
<td>1</td>
<td>CYP3A4 and non-CYP metabolism in liver to active metabolites.</td>
<td>28 to 84 190 (older adults)</td>
</tr>
</tbody>
</table>

Data on drug metabolism and activity of metabolite(s) are for assessment of potential for CYP drug interactions and risk of accumulation. Risk of accumulation is greater, and dose reduction necessary, for older or debilitated adults and for patients with renal or hepatic insufficiency.

* Range of usual **total** daily dose for treatment of adults with anxiety or panic disorder typically given in divided doses two to four times daily.
¶ Important: Data shown are approximate equal potencies relative to lorazepam 1 mg orally and are NOT recommendations for initiation of therapy or for conversion between agents.
Δ Half-life of parent drug and pharmacologically active metabolite, if any.
◊ Not available in US.
§ Range of usual hypnotic dose for adults, given at bedtime.

Graphic 65653 Version 10.0
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Conflict of interest policy