Acute pain management

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Definition of pain

Pain

An Unpleasant Sensory and Emotional Experience Associated with Actual or Potential Tissue Damage, or Described in Terms of Such Damage.

Acute pain

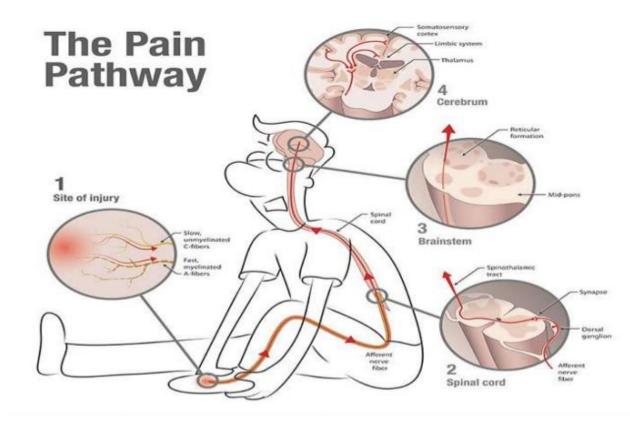
The normal, predicted, physiological response to adverse

chemical, thermal or mechanical stimulus.

Acute pain

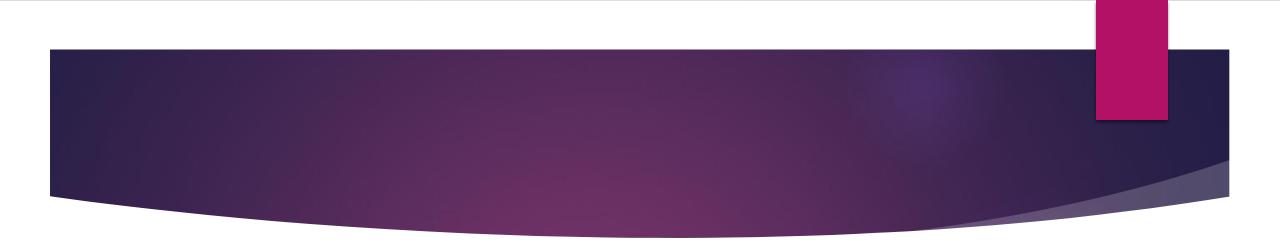
- Pain in Perioperative Setting
- Pain in Patients with Severe or Concurrent Medical Illnesses (Pancreatitis)
- Acute Pain Related to Cancer or Cancer Treatment
- Labor Pain



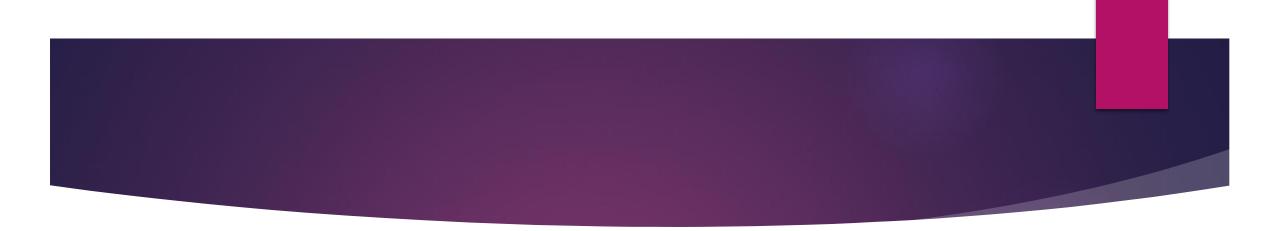


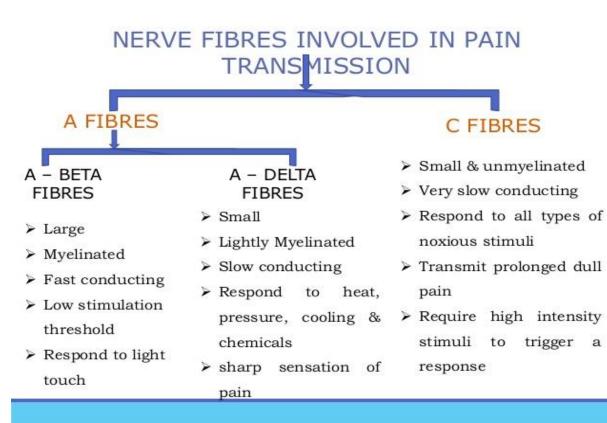
Pain Pathway

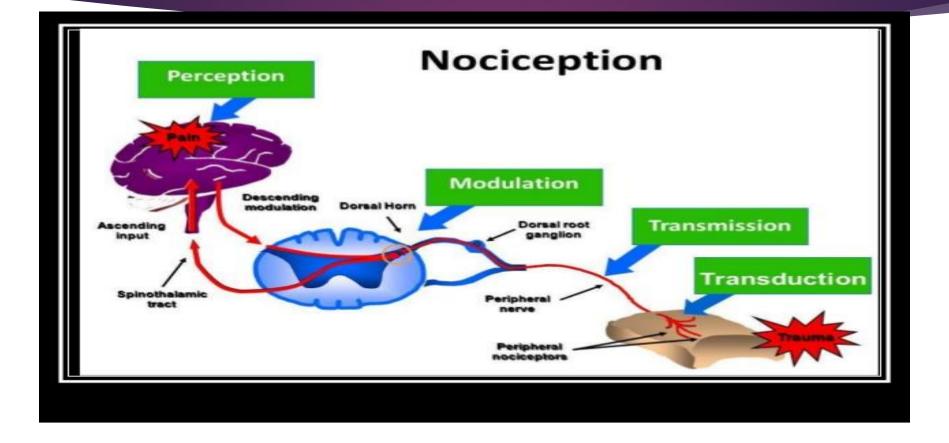
- The nociceptive pathway is an afferent three-neuron dual ascending (eg. Anterolat. and dorsal column medial leminiscal pathway) system, with descending modulation from the cortex, thalamus, brainstem.
- Nociceptors are free nerve endings located in skin, muscle, bone and connective tissue with cell bodies located in the dorsal root ganglia.



- First-order neurons-periphery as A_delta & polymodal C fibers.
- ► A-delta fibers : first pain sharp or stinging well localized.
- Polymodal C fibers :second pain diffuse







Elements of pain

► Transduction:

event whereby noxious thermal ,chemical , or mechanical stimuli are converted into an action potential.

► Transmission:

when the action potential is conducted through the nervous system via the first, second & third-order neurons, which have cell bodies located in DRG, dorsal horn, and thalamus.

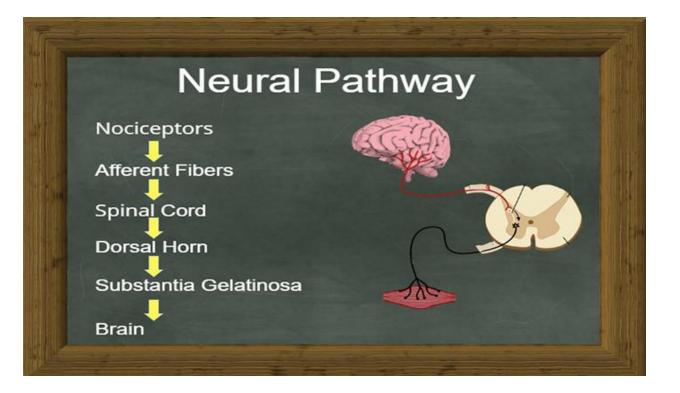


Modulation:

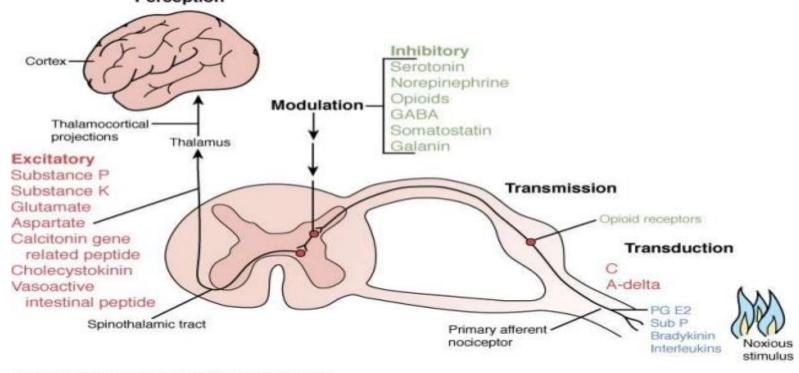
altering afferent neural transmission along the pain pathway.it can involve either inhibition or augmentation of the pain signals.

Perception : final common pathway, which results from the integration of painful input into the somatosensory and limbic cortices.









Source: Mattox KL, Moore EE, Feliciano DV: Trauma, 7th Edition: www.accesspharmacy.com Copyright @ The McGraw-Hill Companies, Inc. All rights reserved.



Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (i.e., substance P and calcitonin gene-related peptide) in the periphery induces vasodilatation and plasma extravasation.



Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones.

Sensitization of peripheral nociceptors may occur and is marked by:

- A decreased threshold for activation
- Increased rate of discharge with activation
- Increased rate of basal (spontaneous) discharge
- Intense noxious input from the periphery may also result in central sensitization (persistent postinjury changes in the CNS that result in pain hypersensitivity) and hyperexcitability (exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage)

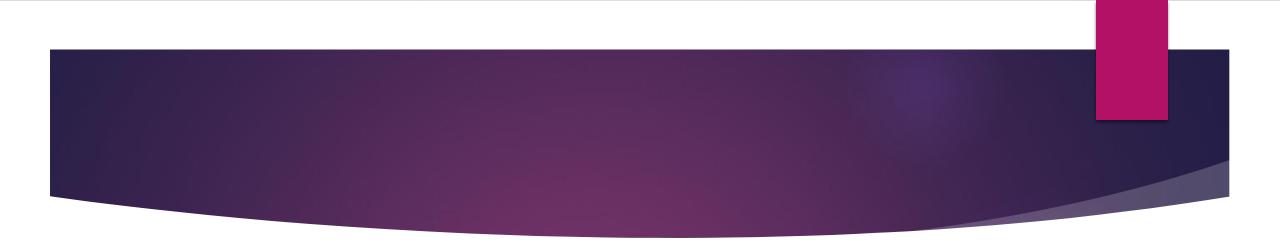


Effects of pain

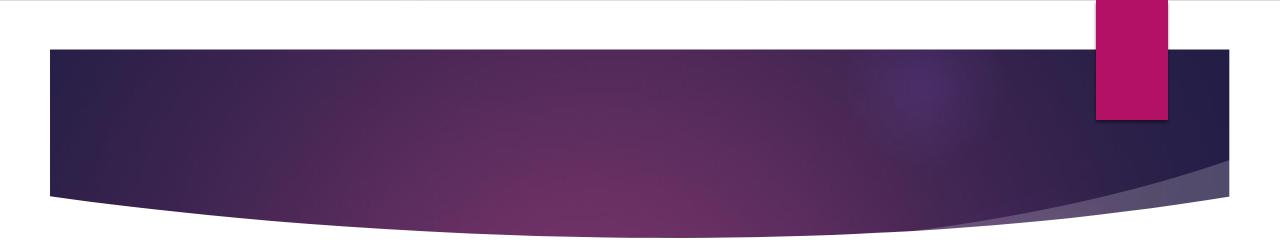
- ✓Increased heart rate
- ✓ Diaphoresis
- √increased blood glucose levels

- ✓ dilatation of pupils
 ✓ decreased GI motility
 ✓ increased musle tension
- ✓ increased respiratory rate

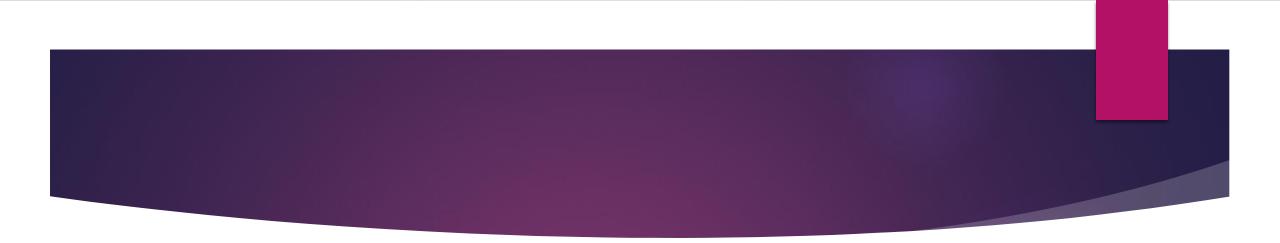




- The neuroendocrine stress response may potentiate detrimental physiologic effects in other areas of the body:
- Hypercoagulability (deep venous thrombosis, vascular graft failure, and myocardial ischemia)
- Immunosuppression
- Hyperglycemia
- Sympathetic activation (myocardial ischemia and infarction)
- Delayed return of postoperative gastrointestinal motility



- Such noxious input may lead to functional changes in the dorsal horn of the spinal cord.
- It seems that certain receptors (e.g., N-methyl-D-aspartate [NMDA]) may be especially important for the development of Chronic pain after an acute injury, although other neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C-γ) may also play important roles in spinal cord sensitization and chronic pain.



- Animal and clinical studies demonstrate that acute pain may quickly transition into chronic pain.
- Noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization) in the dorsal horn of the spinal cord within

one hour and these changes are sufficient to alter behavior within the same timeframe.

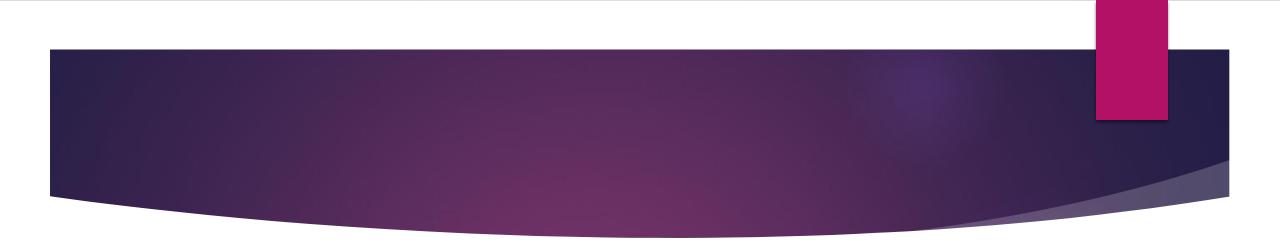
Acute perioperative pain

- Pain that is Present in a Surgical Patient Because of Preexisting Disease, the Surgical Procedure, or a Combination of Both.
- The Incidence of Moderate to Severe Pain with Cardiac, Abdominal, and Orthopedic Inpatient Procedures has been Reported as High as 25%-50%, and Incidence of Moderate Pain after Ambulatory Procedures is 25% or Higher.

(Studies in normal risk patients found a higher incidence of pneumothorax when the subclavian vein is cannulated, as compared with the IJV (0.5-2% vs. 0.2-0.5%).

Importance of pain management

- Adequate Pain Control
- Reduce the Risk of Adverse Outcomes
- Maintain the Patient's Functional Ability, as well as Psychological Wellbeing
- Enhance the Quality of Life
- Shortened Hospital Stay and Reduced Cost



- Clinical studies also suggest that the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.
- Control of perioperative pain (e.g., preventive analgesia) and the fashion in which it is implemented (e.g., multimodality perioperative management) may be important in facilitating short- and long-term patient convalescence after surgery.

CPSP

- Chronic postsurgical pain (CPSP) is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP.
- Poorly controlled acute postoperative pain may be an important predictive factor.
- Transition from acute to chronic pain occurs very quickly and long-term behavioral and neurobiologic changes occur much earlier than was previously thought.



- Poorly managed acute pain that can produce pathophysiologic processes in both the peripheral and central systems that have the potential produce chronicity.
- Acute pain-induced change in the central nervous system is known as <u>neuronal plasticity</u>.

This can result in sensitization of the nervous system resulting in allodynia and hyperalgesia.

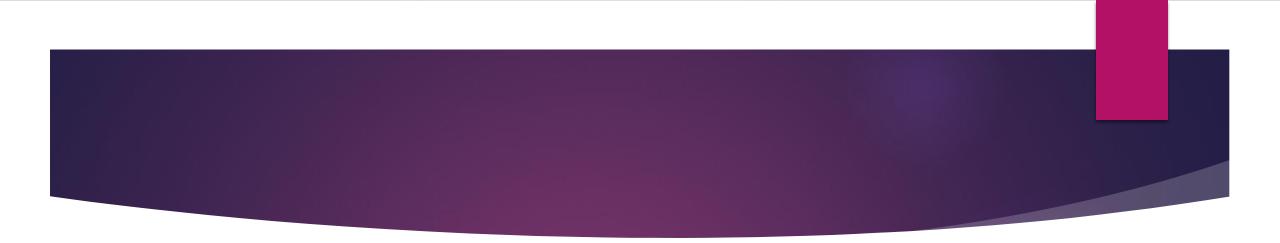


CPSP is relatively common after procedures such as:

- Limb amputation (30% to 83%),
- Thoracotomy (22% to 67%),
- Sternotomy (27%),
- Breast surgery (11% to 57%),
- Gallbladder surgery (up to 56%)

PREEMPTIVE

- Preemptive analgesia referred to an analgesic intervention that preceded a surgical injury
- The precise definition of preemptive analgesia is one of the major controversies in this area of medicine.
- A variety of drugs and techniques have been used to study preemptive analgesia.



- Preventive analgesia is aimed at inhibiting the development of this type of chronic pain.
- This definition broadly includes any regimen given at any time during the perioperative period that is able to control pain-induced sensitization.

Adverse Outcomes Associated with Management of Acute Pain

- Respiratory Depression
- Circulatory Depression
- Sedation
- Nausea and Vomiting
- Pruritus
- Urinary Retention
- Impairment of Bowel Function

Goal

- Pain Management Interventions Should be Offered Around the Clock
- Pain Management is to Provide Continuous Pain Relief
- Patient Should be Assessed for Adequacy of Pain Control

Perioperative evaluation of the patient

- Type of Surgery
- Expected Severity of Postoperative Pain
- Underlying Medical Condition (Respiratory or Cardiac Disease)
- Adjustment or Continuation of Medications (Sudden Cessation may Provoke a Withdrawal Syndrome)
- Treatment to Reduce Preexisting Pain and Anxiety
- Patient and Family Education

Management of acute pain

Pharmacological

Interventional

Pharmacological

- Alter Nerve Conduction (Local Anesthetics)
- Modify Transmission in the Dorsal Horn (Opioids, Antidepressants)
- NMDA receptor antagonist
- Alpha 2 agonist

Routes

► PO

► IM

- Transdermal
- Transmucosal
- Epidural
- Intrathecal

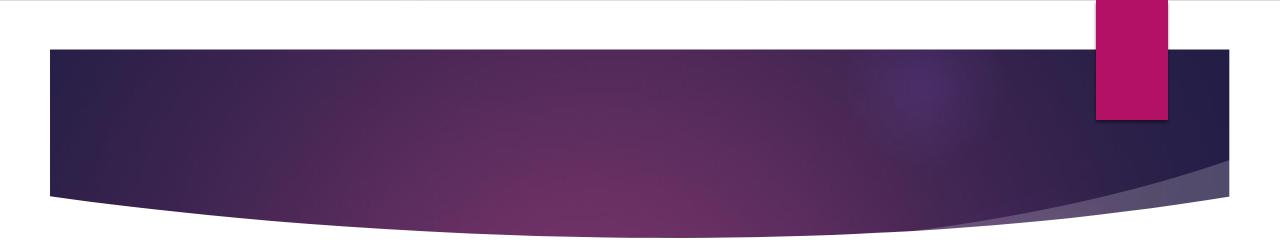
Opioid analgesic

Bind to Opioid Receptors:

Mu, Delta and Kappa

 Morphine, Hydromorphone, Meperidine, Fentanyl, Codeine, Methadone, Oxycodone, Hydrocodone, Tramodol

Opioids may be Combined with NSAIDs to Enhance the Opioid Analgesic Effect



- ► Generally exert their analgesic effects through µ-receptors in the CNS, although there is evidence that opioids may also act at peripheral opioid receptors. There is no analgesic ceiling.
- Opioids may be administered by these routes:

Subcutaneous

Transcutaneous

Transmucosal

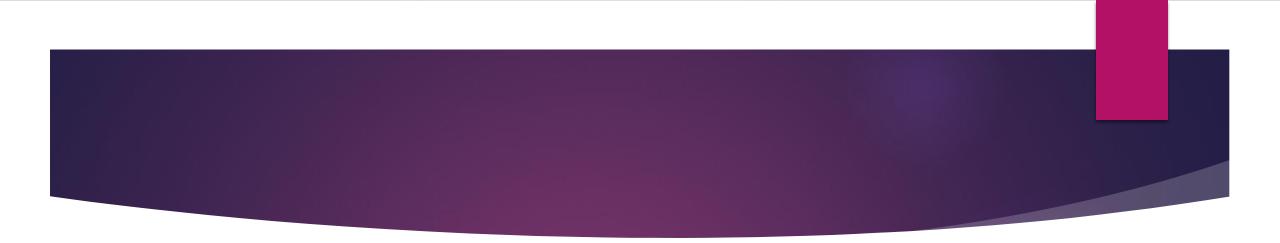
Intramuscular route

Oral

Intravenous

Intrathecal

Epidural space



- There is wide intersubject and intrasubject variability in the relationship of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain.
- In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain.
- The transition from parenteral to oral administration of opioids usually occurs after the patient initiates oral intake and postoperative pain has been stabilized with parenteral opioids.

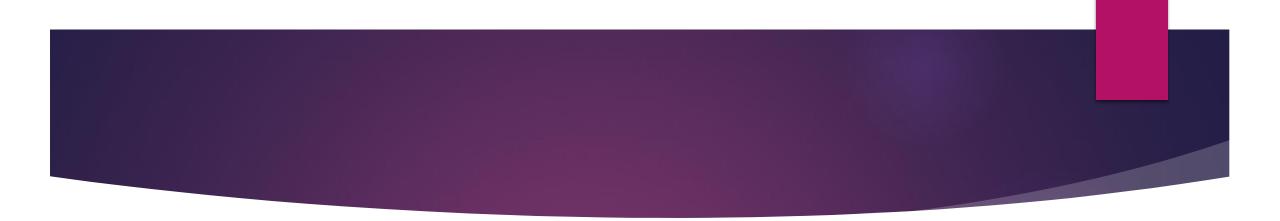
Opioid analgesics

- Equianalgesic Conversion Charts are used when Converting form one Opioid to Another, or Converting from Parenteral to Oral Form
- Respiratory Monitors may be Used Depending on the Patients Age, Coexisting Medical Problems, or Route of Opioid Administered



Conversions: Morphine

OralParenteralEpiduralIntrathecal300100101



Drug	PO mg	IV mg	Starting Oral Dose mg	Comments
Morphine	<mark>30</mark>	10	15-30	MS Contin, Release 8-12 hrs MSIR for BTP
Hydro- morphone	7.5	1.5	<mark>4-8</mark>	Duration Slightly Shorter than Morphine
Meperidine	300	75		Duration Slightly Shorter than Morphine Normeperidine Causes CNS Toxicity
Methadone	20	10	5-10 Qd	Long Half-Life, 24-36 hrs Accumulates on Days 2-3
Fentanyl		0.02- 0.05		Fentanyl Patch, 12 hrs Delay Onset and Offset

Opioid induced Hyperalgesia(OIH)

Relatively "rare phenomenon"

- Patient receiving opioids suddenly and paradoxically become more sensitive to pain despite continued treatment with opioids.
- Remifentanil is the opioid with the highest reported incidence of OIH
- Changing the opioid to a phenyl piperidine such as fentanyl may reduce OIH.
- Evidence of administration of NMDA-R antagonist can abolish OIH.





PCA

- Patient Controlled Analgesia (PCA) uses a programmable syringe pump to allow patients to self-administer their own intravenous analgesia
- PCA was first described in 1968
- In the late 1980's improvements in syringe pump technology allowed PCA to become available for general use.
- Negative-feedback loop

Advantages

- Patients can titrate their analgesia to their pain
- Patients are in "control"
- Rapid response to demand for analgesia
- Reduced patient anxiety compared with other analgesia techniques
- Fewer complications when opioids are administered this way
- Excellent analgesia for the majority of patients
- Increased staff, patient and family satisfaction
- Decreased staff workload

Bolus dose

- When the patient presses the remote button, the PCA delivers the programmed bolus dose
- In cases of severe pain or in patients with large opioid requirements the bolus dose may be several times higher than the usual protocol.
- The optimal demand dose is 1 mg for morphine and 40 µg for fentanyl in opioid-naive patients; however, the actual dose for fentanyl (10 to 20 µg) is often less in clinical practice.

Lockout interval

- Lockout time is usually set at 5 minutes
- The PCA will not deliver a dose during lockout time, even if the patient presses the button
- This allows each bolus to reach peak effect before the patient has another bolus
- Lockout time reduces the risk of overdose.
- The lockout interval is a safety feature of intravenous PCA, and although the optimal lockout interval is unknown, most intervals range from 5 to 10 minutes, depending on the medication in the PCA pump.

Background infusion

- Background infusion (continuous infusion) may be added to improve analgesia
- Generally background infusion is only required for patients following major surgery or patients with oncology-related pain and high opioid requirements
- Background infusions may increase the risk of the side effects associated with opioids:

sedation, respiratory depression, itch, nausea.

- The trials have failed to demonstrate any analgesic benefits of a background infusion in adult opioid-naïve patients.
- There may be a role for use of a background infusion in opioid-tolerant or pediatric patients







Drug	Bolus Dose (mg)	Lock-Out (Minutes)
Morphine	<mark>0.5-2</mark>	5-15
Hydromorphone	0.1-0.2	<mark>5-10</mark>
Fentanyl	0.01-0.02	5-10

Good tries/Bad tries

- A good try is when the PCA delivers a bolus dose of analgesia
- A bad try is when the patient presses the button during the lockout time and no bolus dose is delivered
- Knowing the proportion of good and bad tries allows CPMS to adjust the PCA settings to meet the patient's needs or whether further patient education is required

Dose Duration

- Dose duration is normally set as 'stat'
- The dose duration may be increased to prevent problems such as lightheadedness or nausea associated with a rapid peak of onset of analgesia



- The incidence of opioid-related adverse events from intravenous PCA does not seem to differ significantly from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously.
- The rate of respiratory depression associated with intravenous PCA is low (<0.5%) and does not appear to be higher than that with PRN systemic or neuraxial opioids.
- Factors that may be associated with the occurrence of respiratory depression with intravenous PCA include:
- Background infusion
- Advanced age
- Concomitant administration of sedative or hypnotic agents
- Coexisting pulmonary disease such as sleep apnea
- Errors in programming or administration

Non-Opioid Analgesics

Acetaminophen

- ▶ NSAIDs (Ibuprofen, Ketorolac,
- COX-2 Inhibitors)
- Lidocaine Patch (Lidoderm)

NSAIDs

- Include also aspirin and acetaminophen.
- Inhibit cyclooxygenase (COX) and synthesis of prostaglandins (important mediators of peripheral sensitization and hyperalgesia).
- ▶ NSAIDs can also exert their analgesic effects through inhibition of spinal COX.

► Isoforms:

COX-1 (constitutive): platelet aggregation, hemostasis, and gastric mucosal protection

COX-2 (inducible): pain, inflammation, and fever

COX-3 : may represent a primary central mechanism by which acetaminophen and other antipyretics decrease pain and fever

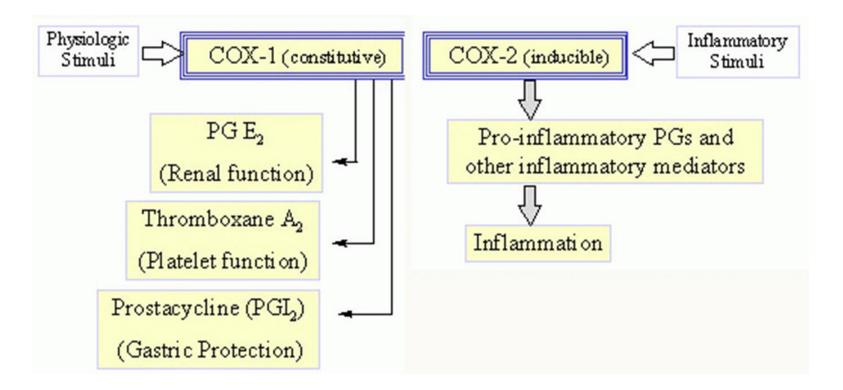
NSAIDs

Relieve of Mild to Moderate Pain

Complication:

- ► GI Discomfort
- ► GI Bleeding (Inhibition of COX-1)
- Nephrotoxicity
- Inhibition of Platelet Aggregation







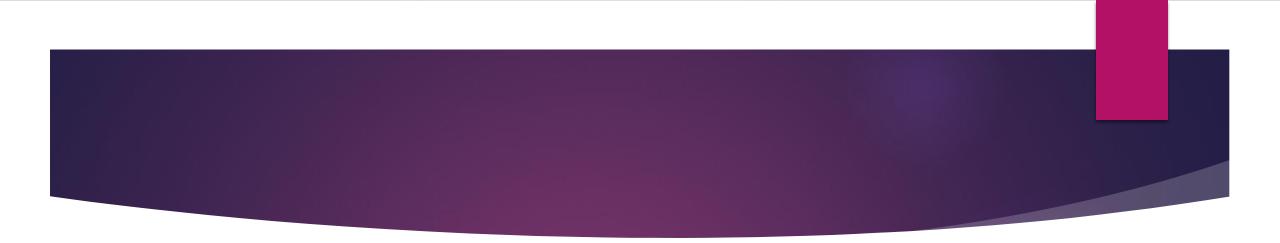
- COX-2 inhibitors are associated with a lower incidence of gastrointestinal complications and exhibit minimal platelet inhibition, even when administered in supratherapeutic doses.
- However, long-term use of COX-2 inhibitors has been associated with excess cardiovascular risk such that rofecoxib was withdrawn from the market

NNT

- The Number Needed to Treat (NNT) is the number of patients you need to treat to prevent one additional bad outcome (death, stroke, etc.). For example, if a drug has an NNT of 5, it means you have to treat 5 people with the drug to prevent one additional bad outcome.
- To calculate the NNT, you need to know the Absolute Risk Reduction (ARR); the NNT is the inverse of the ARR:

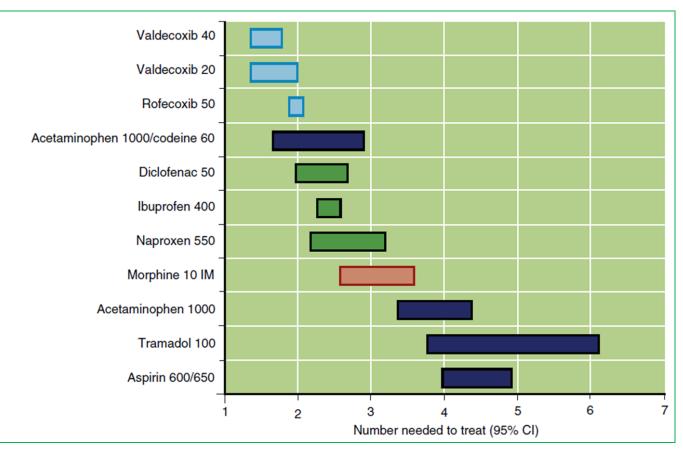
$\blacktriangleright NNT = 1/ARR$

Where ARR = CER (Control Event Rate) – EER (Experimental Event Rate). NNTs are always rounded up to the nearest whole number.



- The ARR is therefore the amount by which your therapy reduces the risk of the bad outcome. For example, if your drug reduces the risk of a bad outcome from 50 per cent to 30 per cent, the ARR is:
- ► ARR = CER EER = 0.5 0.3 = 0.2 (20 per cent)
- ▶ therefore
- ▶ NNT = 1/ARR = 1/0.2 = 5





ketorolac

- Potent Analgesic
- Parenteral (IV or IM)
- ▶ 15-30 mg Q 6hr
- Patients Older than 16 yrs
- Should not Exceed 5 days

Gabapentanoids

Gabapentin and pregabalin

- Antiepileptic drugs also used in the treatment of neuropathic pain
- Interact with calcium channel a2-8 ligands to inhibit calcium influx and subsequent release of excitatory neurotransmitters.
- ► Oral pregabalin is absorbed more rapidly and has more absolute bioavailability (≥90% versus <60%) than does gabapentin.</p>



- Oral gabapentin improves the analgesic efficacy of opioids both at rest and with movement, and reduces opioid consumption and opioid-related side effects, but with an increased incidence of side effects such as sedation and dizziness.
- Considered as part of a multimodal approach to postoperative analgesia.
- Perioperative administration of gabapentin and pregabalin may reduce the incidence of CPSP.

KETAMIN

- NMDA-antagonistic properties may be important in attenuating central sensitization and opioid tolerance.
- Subanesthetic doses
- Have reduced 24-hour PCA morphine consumption and postoperative nausea or vomiting and had minimal adverse effects.
- Does not appear to cause hallucinations or cognitive impairment.
- The incidence of side effects, such as dizziness, itching, nausea, and vomiting, is comparable to that seen with opioids.
 - Can theoretically be useful in attenuating central sensitization and potentiating the analgesic effect of epidural opioids, but additional safety and analgesic data are needed.

TRAMADOL

- Synthetic opioid
 - Weak µ-agonist activity
 - Inhibits reuptake of serotonin and norepinephrine
- Central mechanisms as well as peripheral local anesthetic properties
- For moderate postoperative pain
- Relative lack of respiratory depression, major organ toxicity, and depression of gastrointestinal motility



- Low potential for abuse
- Common side effects: dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache.
- Tramadol should be used with caution in patients with seizures or increased intracranial pressure and is contraindicated in those taking monoamine oxidase inhibitors.

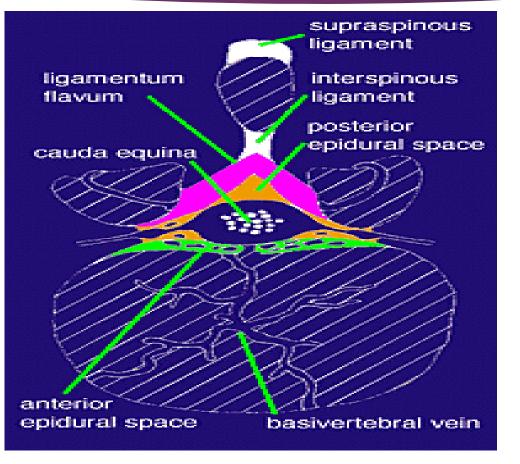
Lidoderm

- ▶ 5% Lidocaine Patch
- Indicates for Pain Relief in Post-herpetic Neuralgia
- Each Patch Contains 700 mg of Lidocaine
- Should be Applied to Intact Skin
- About 3% is Absorbed
- ▶ 1-3 Patches Once a Day for 12 hrs

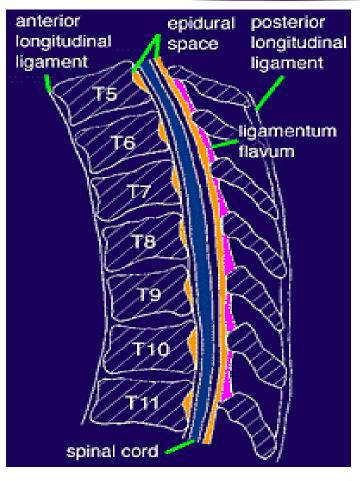
Interventional managment

- Epidural Analgesia (Continuous Lumbar or Thoracic Epidural Catheter Placement, PCEA)
- Spinal Analgesia
- Peripheral Nerve Block (Single Shot or Continuous)

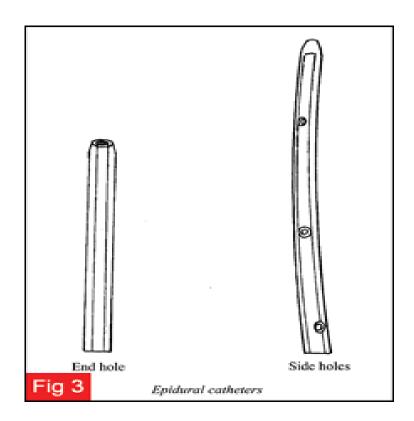






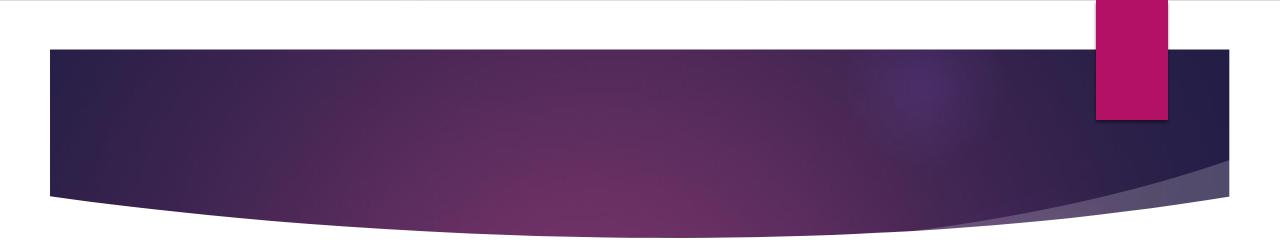






Epidural Anesthesia

- Anesthestizes the Emerging Nerve Roots of the Spinal Cord
- Epidural Injection of Anesthetic Produces a Regional Dermatomal "band" of Anesthesia Spreading Cephalad and Caudad from the Site of Injection
- Level of Anesthesia Depends on :
- Volume of the Drug
- Level of Injection



- Lumbar Epidural: Lower Extrimity, Pelvic, and Lower Abdominal Procedures
- Thoracic Epidural: Upper Abdomen and Thoracic Procedures
- Caudal Injection: More Commonly Used for Pediatric Patients (Genitourinary and Lower Abdominal Procedures

Hydrophilic opioid morphin

Slow Onset, Long Duration, High CSF SolubilityAdvantages

- Prolonged Single Dose Analgesia
- Thoracic Analgesia with Lumbar Administration
- Minimal Dose Compared with IV Administration

Disadvantages

- Delayed Onset of Analgesia
- Unpredictable Duration
- Delayed Respiratory Depression

Lipophilic Opioids Fentanyl

Rapid Onset, Short Duration, Low CSF SolubilityAdvantages

- Rapid Analgesia
- Ideal for Continuous Infusion or PCEA

Disadvantages

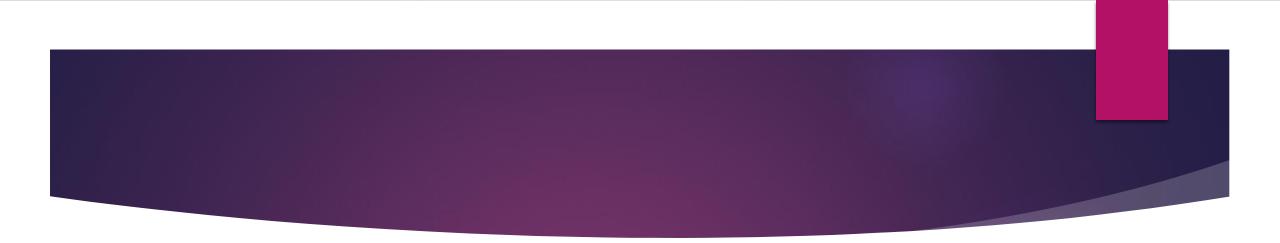
- Systemic Absorption
- Brief Single Dose Analgesia
- Limited Thoracic Analgesia with Lumbar Administration

Table 87-3 Properties of Neuraxial Opioids

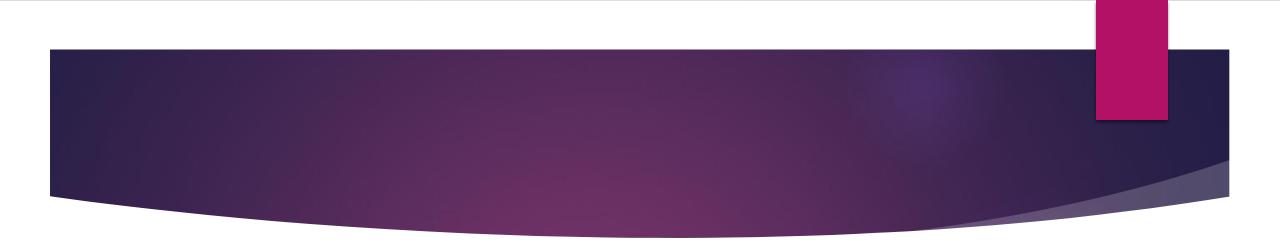
Property	Lipophilic Opioids	Hydrophilic Opioids
Common drugs	Fentanyl, sufentanil	Morphine, hydromorphone
Onset of analgesia	Rapid onset (5-10 min)	Delayed onset (30-60 min)
Duration of analgesia*	Shorter duration (2-4 hr)	Longer duration (6-24 hr)
CSF spread	Minimal CSF spread	Extensive CSF spread
Site of action	Spinal ± systemic	Primarily spinal
Side effects Nausea and vomiting Pruritus	Lower incidence with hydrophilic opioids Lower incidence with hydrophilic opioids	
Respiratory depression	Primarily early; minimal delay	Both early (<6 hr) and delayed (>6 hr) possible

CSF, cerebrospinal fluid.

*The duration of analgesia varies.



- Single-dose epidural administration of lipophilic and hydrophilic opioids is used with the same considerations as for intrathecal use.
- Diluting the epidural dose of fentanyl (typically 50 to 100 µg) in at least 10 mL of preservative- free normal saline is suggested to decrease the onset and prolong the duration of analgesia.
- Single-dose hydrophilic opioid (e.g. morphine) may be especially helpful in providing postoperative epidural analgesia when the epidural catheter's location is not congruent with the surgical incision (e.g., lumbar epidural catheter for thoracic surgery).
- Lower doses of epidural morphine may be required for elderly patients and thoracic catheter sites.



- An extended-release formulation of (single-dose) epidural morphine encapsulated within liposomes that results in up to 48 hours of analgesia has recently been introduced.
- Precautions:
- ▶ The vial should be gently inverted before withdrawal of the medication.
- Increase the interval between administration of local anesthetic (including test doses) and liposomal extended-release morphine to at least 15 minutes.
- It should be administered within 4 hours after withdrawal from the vial.
- A lower dose should be administered to the elderly or those with decreased physiologic reserve or coexisting disease.
- It has not been studied or approved in pediatric patients.



- Placement of thoracic epidural catheters appears to be relatively safe, and there is no evidence of a higher incidence of neurologic complications with placement of a thoracic (versus lumbar) epidural catheter.
- The benefits of epidural analgesia in decreasing morbidity in patients undergoing abdominal and thoracic surgery are seen only with thoracic (congruent), not lumbar (incongruent) epidural catheter placement.

Location of Catheter Insertion

- Insertion of the epidural catheter congruent to the incisional dermatome (i.e., catheter-incision-congruent analgesia) results in optimal postoperative epidural analgesia by infusing analgesic agents to the appropriate incisional dermatomes, providing superior analgesia, decreasing drug requirements, minimizing side effects (e.g., lower extremity motor block and urinary retention), and decreasing morbidity.
- Use of a high thoracic epidural does not inhibit sympathetic nerve activity in the lower extremities, which are supplied by sympathetic nerve fibers from T9 to L1.

PCEA

- Technique that Allows Basal Infusion and Demand Boluses into the Epidural Space
- Solutions Used:
- Local Anesthetics: 0.05-0.125% Bupivacaine
- Opioids: Morphine 50 mcg/ml
- Hydromorphone 10 mcg/ml
- Fentanyl 2-5 mcg/ml



- Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with intravenous PCA and may provide analgesia superior to that with the use of a demand dose alone.
- In general, most acute pain specialists have gravitated toward a variety of low-concentration local anesthetic-opioid combinations.
- A lipophilic opioid is usually chosen because its rapid analgesic effect and shorter duration of action may be more suitable for use with PCEA.



- Failure of Block (Patchy or Unilateral Block)
- Injury to Nerve
- Infection
- Epidural Hematoma or Abscess
- Dural Puncture (Total Spinal or PDPH)

Complication

- Side Effect of Drugs in Epidural Space
- Hypotension Secondary to Sympathetic Blockade
- Intravascular Injection (Local Anesthetic Toxicity)
- Respiratory Depression
- Sedation
- Bladder Distention
- Difficulty in Ambulation

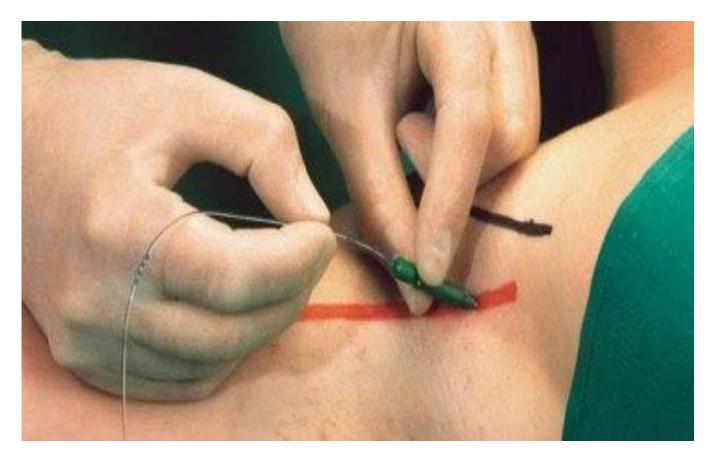
Peripheral nerve block

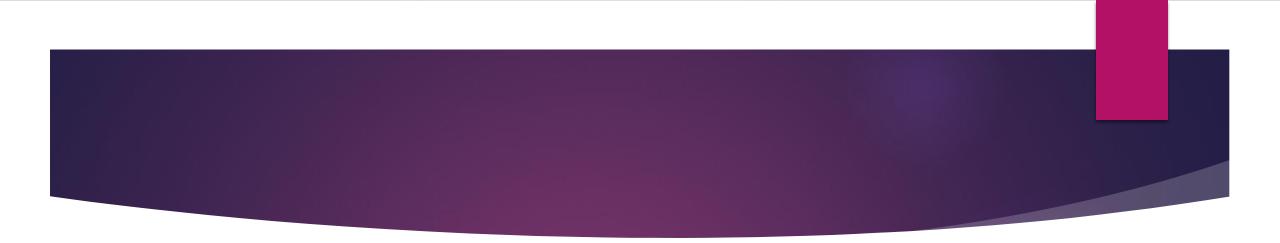
- Anesthetizing the Nerve that is Innervating Surgical or Painful Area
- Single Shot or Continuous Infusion through Catheter
- Upper Extrimity: Brachial Plexus, Median, Ulnar or Radial Nerve
- Lower Extrimity: Sciatic, Femoral, Posterior Tibial, Sural, Saphenous, Deep and Superficial Peroneal Nerve
- Intercostal Nerve Block
- Surgical Wound Infiltration of Local Anesthetic







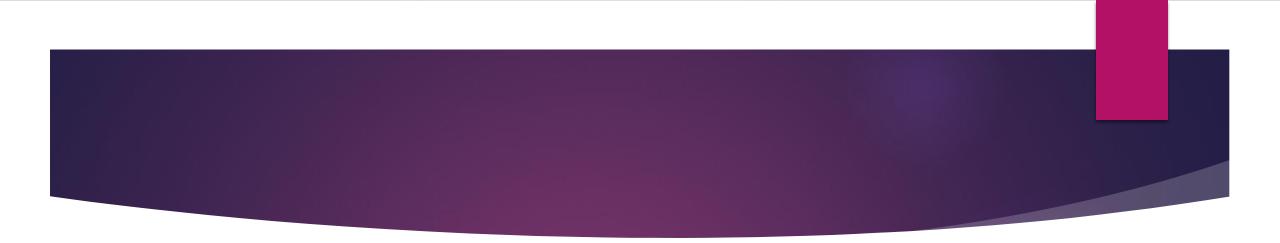




- The duration of postoperative analgesia resulting from a single injection of the local anesthetic in the peripheral nerve block varies but may last up to 24 hours after injection.
- Continuous infusions or Patient-controlled peripheral analgesia
- When compared with systemic opioids:
- Superior analgesia
- Decreased opioid-related side effects
- Greater patient satisfaction

Other Techniques

- Transcutaneous electrical nerve stimulation (TENS)
- Acupuncture
- Psychological approaches
- Mechanism of analgesia by TENS may be related to modulation of nociceptive impulses in the spinal cord, release of endogenous enkephalins, or a combination of these and other mechanisms.
- TENS and acupuncture may provide postoperative analgesia, decrease postoperative opioid requirements, reduce opioid-related side effects, and attenuate activation of the sympathoadrenal system.



The differential behavior response to surgical incision may be related to global (i.e., personality, gender, age, and culture) and specific (i.e., fear, depression, anger, and coping) psychological factors.

Cognitive behavior therapy

Although the placebo effect has traditionally been thought to have a psychological origin, the placebo response may exert part of its effects through activation of endogenous opioids and be useful in reducing the intensity of pain.



