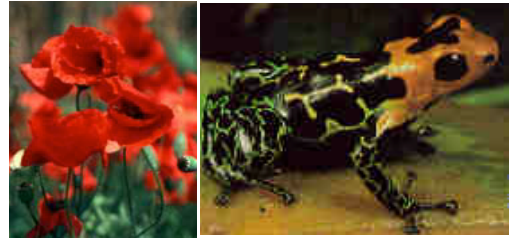# OPIOID ANALGESICS
BMS 255
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Reading: Goodman and Gilman Chapter 18   p480-525

"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." (Sydenham, 1680)

Poppy
(opiates)

South American tree frog
(peptide)

Objectives:

> **Opioids** produce a powerful and selective reduction in the human and animal response to a strong and otherwise noxious stimulus and alter the clinical pain state. The purpose of these lectures is to enable the student to understand:
> - The molecular interactions of drugs with specific opioid receptors and their subclasses
> - The pharmacodynamics of opioid agonists, partial agonists, and antagonists
> - Where and how opioids act to produce analgesia
> - The nuances of opioid action that define their side effect profiles.
> - The therapeutic implementation of opioid drugs

Lecture Outline:
A.   Terminology.
B.   Opioid receptors.
C.   Receptor coupling.
D.   Opioid pharmacodynamics.
E.   Endogenous opioid peptides.
F.   Opioid analgesia.
G.   Nonanalgesic effects mediated by opioids.
H.   Opioid drugs.
I.   Drug interactions.
J.   Clinical use of opioids as analgesics.
K   Analgesics: general principles governing use.
L.   Tolerance/dependence and addiction.
M.   Ethical issues in opioid use.
N.   Summary of important drugs.

Lecture Notes:
A.   Terminology.
1.   The term **opiate** is used to describe alkaloid molecules derived from opium, which in turn is derived from the juice of the opium poppy *Papaver somniferum*. Examples include morphine and codeine.

2**.**   The term **opioid** refers to all compounds which have functional properties like the opiates; the opioid category includes not only the opiates but also semi-synthetic non-alkaloids and even endogenous peptides.

B.   Opioid receptors.
1. Historical basis for definition of an opioid receptor (1850-1975).

- Extraction/purification of active poppy ingredient: morphine (Serterner, 1850s).

- Effects: respiratory depression, somnolence, analgesia, decreased GI motility.

- Agonist structure-activity relationships: morphine $\geq$ meperidine > codeine > 0

- Structurally similar agents (e.g., naloxone) act as antagonists; have no effect alone but reverse the effects of an agonist.

- Opioid binding studies indicated high affinity binding sites.

These observations suggested a specific **opioid receptor**. Thus, an **opioid** can be defined more precisely as a substance that produces the above-listed effects by acting at opioid receptors and whose actions are reversed by naloxone.

2. Opioid receptor types (Table 1).
At present, three types of opioid receptors have been identified: **mu (µ) receptors**, **delta (∂) receptors**, and **kappa (κ) receptors**. These receptor types are defined by:
- Agonist structure-activity relationships in bioassay (ability to block stimulated contraction of specific smooth muscle tissues) and binding (Table 1).
- Antagonist activity profile: naloxone blocks all opioid receptors (Table 1).
- Lack of cross-tolerance.
- Cloning.

Table 1. Summary of Opioid Receptor Types

Receptor	Bioassay	Representative Agonists	Antagonists
Mu (µ)	Guinea pig ileum	Morphine, Hydromorphone, Fentanyl * ß-Endorphin**	Naloxone* ß-Funaltrexamine
Delta (δ)	Mouse vas deferens	DPDPE Leu-enkephalin** ß-Endorphin**	Naloxone* Naltrindole
Kappa (κ)	Rabbit vas deferens	Butorphanol* Dynorphin 1-17**	Naloxone* Nor-BNI

Abbreviations: DPDPE, synthetic enkephalin derivative; nor-BNI, nor-binaltorphimine.

*Clinically relevant   ** Endogenous peptides

In addition to μ, ∂, and κ receptors, there are two other receptor types that have been historically associated with the opioids but are ***not*** in fact opioid receptors:
- **Sigma (σ) receptors** can be stimulated by opioids and may account for the excitatory actions of opioids; however, these excitatory effects probably are produced by an interaction with the phencyclidine (PCP) binding site on the NMDA receptor. Naloxone does *not* block these receptors.

- **Orphan opioid receptor-like (ORL) receptors** are structurally similar to the μ opioid receptor but are insensitive to opioid ligands, including naloxone.

3. Opioid receptors (μ, ∂, κ) have several common properties:
- Each receptor is encoded by a separate single gene.
- 370-400 amino acids.
- Significant μ, ∂, κ receptor protein sequence homology (>75%).
- All are GPCRs with seven transmembrane-spanning regions (Figure 1).
- Extracellular N terminus.
- Third intracellular loop with multiple amphipathic α-helices.
- 2-5 glycosylation sites.
- All are negatively coupled to adenylyl cyclase via $G_{i/o}$.
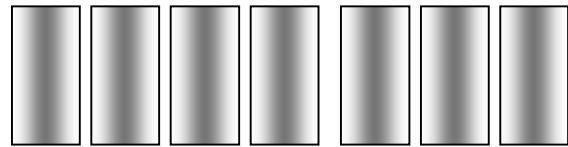- Many splice variants have been identified for the μ receptors; others likely.

Figure 1. Heptahelical transmembrane-spanning, G protein-coupled opioid receptor.

4. Opioid receptor subtypes.
- Based on pharmacological evidence (differential agonist and antagonist structure-activity relationships), several subtypes have been hypothesized for the μ, ∂, and κ opioid receptors.
- With extensive low-stringency hybridization procedures, no opioid receptor types other than the cloned μ, ∂, and κ opioid receptors have been isolated.
- Alternatives leading to multiple subtypes.
  - Single nucleotide polymorphisms in receptor protein.
  - Hetero-oligomerization can create μ-∂, μ-κ, and ∂-κ receptor complexes.

C. Receptor coupling.
1. Intracellular signaling (Figure 2).
- Majority of opioid receptor-mediated effects are blocked by pertussis toxin (PTX), indicative of role of G_i/G_o protein (Figure 2).
- μ, ∂, and κ receptor activation induces GTP binding to the G_i/G_o subunits.

- G_z, a PTX-insensitive member of the G_i subfamily of G proteins, can inhibit cAMPand may substitute for the G_i/G_o subunits.
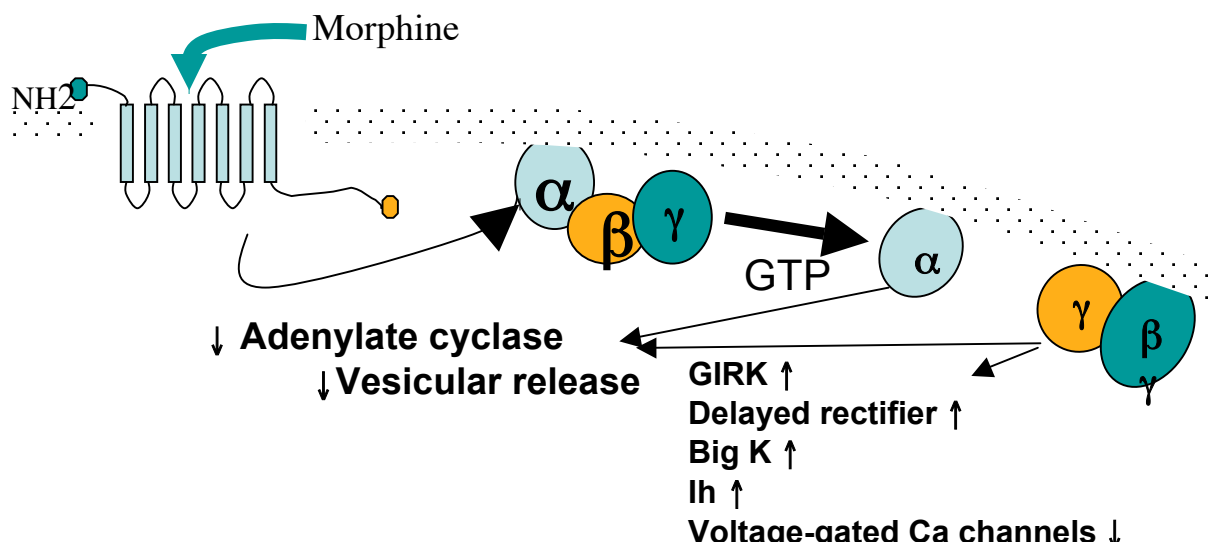

Figure 2. Schematic indicating the sequence of events whereby a G protein-coupled receptor inhibits adenylyl cyclase and affects a variety of channels that lead to hyperpolarization of the membrane (by increasing conductance through the GIRK, delayed rectifier, big K, and Ih K$^+$ channels) and decreased transmitter release (by blocking the activation of the voltage-gated Ca^{2+} channels).

2. Receptor coupling.

   Agonist occupancy of opioid receptors typically leads to several events that serve to inhibit the activation of the neuron (Figures 2 and 3).

   - Inhibition of adenylyl cyclase.
   - Inhibition of the activation of voltage-gated Ca^{2+} channels, which will depress neurotransmitter release.
   - Membrane hyperpolarization by increasing K$^+$ conductance, principally by activating a G protein-activated inwardly rectifying K$^+$ channel (GIRK), resulting in reduced excitability of soma. These effects lead to a powerful, receptor-mediated inhibition of synaptic function (Figure 3).
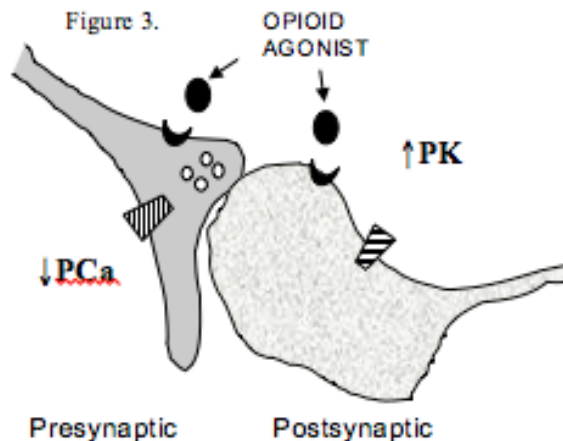
3. Receptor internalization.

   Receptor trafficking initiated by agonist binding and internalization through the endosomal pathway may be involved in desensitization and/or initiation of nuclear signaling (Figure 4). The carboxy-terminal tail of opioid receptors, like that of other GPCRs, regulates the extent and efficiency of internalization.

- Agonist binding to the opioid receptor results in the rapid phosphorylation of the

carboxy-terminal tails of the opioid receptors by GPCR kinases (GRKs).
- Phosphorylation increases the affinity of the GPCR for ß arrestin.
- Arrestin-bound complex recruits c-Src adaptor proteins (AP-2 complex).
- AP-2 complex links ß arrestin and clathrin to promote endocytosis.
- Association of ß arrestin with the receptor uncouples the receptor from the respective G protein that transduces the signal and thus blunts receptor signaling (an example of receptor desensitization).
- Internalization is dependent upon agonist and receptor:
  μ opioid receptor: etorphine = methadone >>>> **morphine** = DPDPE = 0
 ∂ opioid receptor: DPDPE >>>>>> **morphine** = DAMGO = 0

Difference between morphine and other mu agonists regarding internalization is that morphine doe not activate ß arrestin.

Figure 4. Sequence of events that enables agonist occupancy to initiate internalization of opioid receptors.
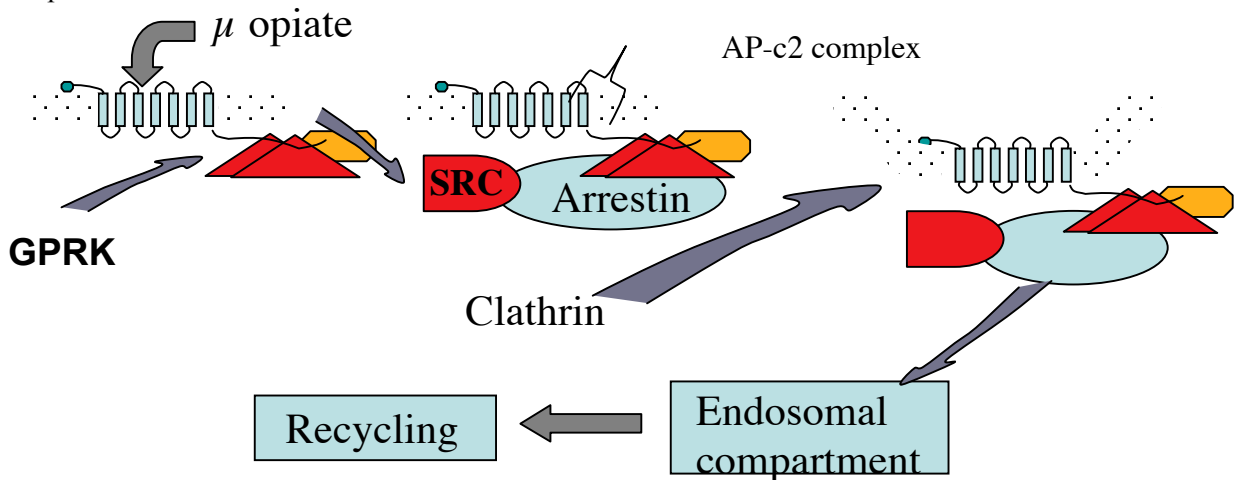
D. Opioid pharmacodynamics.

1. Drug intrinsic activity (Figure 5).
   Opioids may be agonists, partial agonists, or antagonists. A drug that binds competitively at a receptor and produces a concentration-dependent activation of the receptor is called an **agonist**. Drugs differ in their ability to activate a receptor:
   - For a given level of receptor occupancy, an agonist "A" that produces a greater effect than an agonist "B" is said to have greater **intrinsic activity**.

Figure 5.

A: Agonist
B: Partial agonist
C: Antagonist

EFFECT (%)

LOG [DRUG CONC]
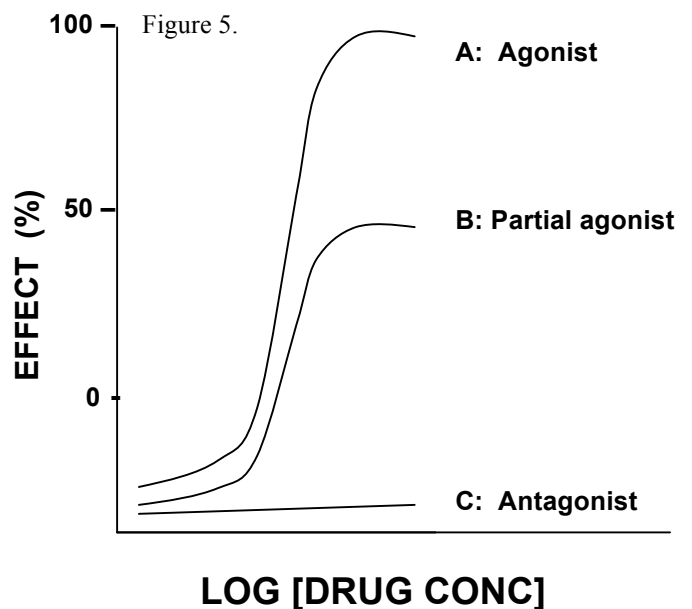
- Conversely, in this situation, "B" is said to be a **partial agonist** relative to "A."
- An agent "C" that has affinity for the receptor but no intrinsic activity is said to be an **antagonist**.
- Some molecules can have some affinity at several receptors and act as an agonist at one and as an antagonist at another (e.g., nalorphine is an agonist at κ receptors and an antagonist at μ receptors).
- If two agents act at the same receptor but differ in intrinsic activity, the agent with lower intrinsic activity will act to antagonize the effect of the agent with higher intrinsic activity (e.g., buprenorphine will antagonize morphine).

Table 2. Pharmacodynamic Summary of Representative Opioid Ligands

| Drug	μ Receptors	κ Receptors	∂ Receptors
Morphine	**Agonist**	**Partial agonist**	**No effect**
Buprenorphine	**Partial agonist**	**No effect**	**No effect**
Naloxone	**Antagonist**	**Antagonist**	**Antagonist**
Butorphanol	**No effect**	**Agonist**	**No effect**
Nalorphine	**Antagonist**	**Agonist**	**--**
Pentazocine	**Antagonist**	**Agonist**	**--**
Etorphine	**Agonist**	**Agonist**	**Agonist**

E. Endogenous opioid peptides.
A variety of endogenous materials are found that can interact with opioid receptors and the effects of which are reversed by naloxone. These endogenous compounds are <u>peptides</u>.

1. Prohormones and peptides (Figure 6).
   - Three principal classes of endogenous opioid peptides have been identified: the **enkephalins**, the **endorphins**, and the **dynorphins**. The peptides in each class are derived from a distinct prohormone (see below).

   - In each case, the prohormone undergoes post-translational cleavage to form discrete smaller, biologically active peptides that are agonists at opioid receptors (Table 3).

   - These prohormones are characterized by the encryption of multiple pentapeptide sequences. As shown in Figure 6, each of the prohormones contains one or more copies of the pentapeptides **met-enkephalin** and/or **leu-enkephalin**. The sequences of these pentapeptides are as follows:
     o **Met enkephalin: Y-G-G-F-M**
     o **Leu enkephalin: Y-G-G-F-L**
     The pentapeptide sequences are set off by pairs of basic amino acids (lysine, arginine), e.g., -**K-R-Y-G-G-F-M- R-R-** .

   - The peptides are cleaved from the prohormone by trypsin-like enzymes and carboxypeptidases to create fragments with free amino termini and extended carboxy termini, e.g., **Y-G-G-F-M……..** .

Figure 6. Three opioid prohormones. Black block indicates embedded met-enkephalin pentapeptide sequence (Y-G-G-F-M), while open block indicates leu-enkephalin pentapeptide sequence (Y-G-G-F-L).

Proenkephalin

Pro-opiomelanocortin

Prodynorphin
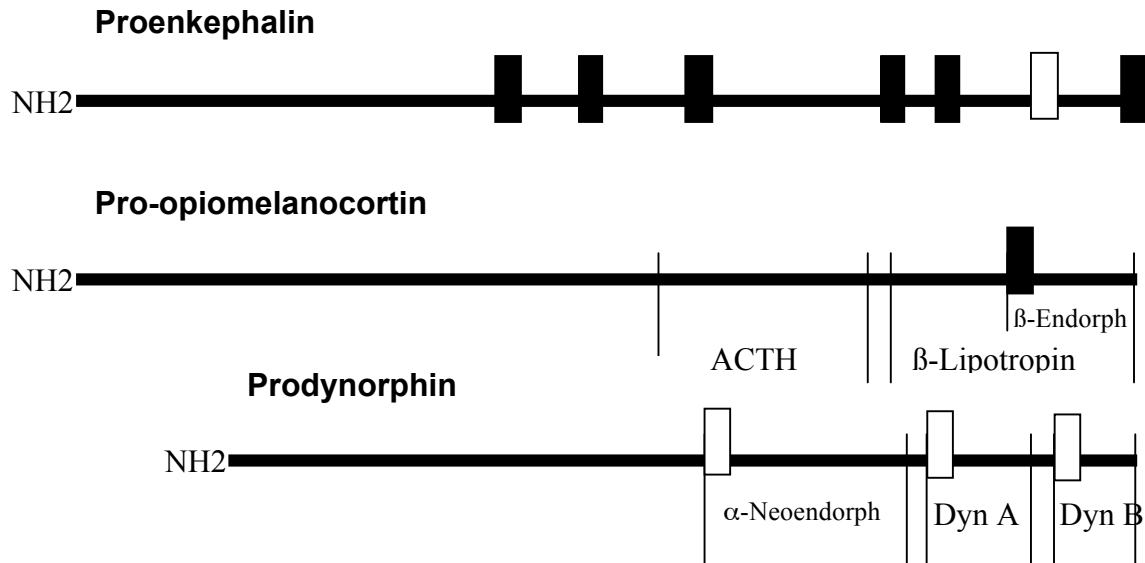
- The prohormones for the three peptide classes are as follows (Figure 6):
  1) Proenkephalin (**enkephalin** prohormone).
     - Prohormone contains multiple copies of met-enkephalin and one copy leu-enkephalin.
     - Found in brain, in multiple populations of interneurons/long tracts.
     - Adrenal chromaffin cells are the primary source of circulating enkephalins.
  2) Pro-opiomelanocortin (POMC) (**endorphin** prohormone).
     - Prohormone contains sequences for adrenocorticotrophin (ACTH); ß-lipotropin (ß-LPH), and α-melanocyte-stimulating hormone (α-MSH). ß- lipotropin is cleaved to form ß-endorphin (31 amino acids).
     - Found in pituitary; processed and secreted, source of circulating ß-endorphin.
  3) Prodynorphin (**dynorphin** prohormone).
     - Multiple copies of leu-enkephalin with extended sequences, e.g., dynorphin 1-13: Y-G-G-F-L-R-R-I-R-P-K-L-K.
     - Found in pituitary/adrenal (small amounts

2. Receptor affinities.
   Endogenous peptides have a broad range of affinities for three opioid receptors (Table 3).

Table 3. Receptor Affinities of Endogenous Opioids

Endogenous Opioid	μ	∂	κ
Met-enkephalin	+	+++	0
Leu-enkephalin	+	+++	0
ß-Endorphin	+++	++	0
Dynorphin 1-13	0	0	+++

3. Physiological role of endogenous opioids.
    Stress releases endogenous opioids in the brain and in the periphery from the pituitary and adrenal medulla.
    > Runners high? Endogenous pain control?
    > Endogenous modulation of respiration/cardiovascular function?

    While it is clear that these products are present and are released, it is important to emphasize that naloxone alone in humans has modest effects suggesting that the modulatory effects of endogenous opioids are subtle. Opioid antagonists such as naloxone or naltrexone have been shown to (modestly):

    1. Reduce hypotension during septic and hemorrhagic shock.
    2. Increase respiratory rate during hypoxia
    3. Increase unpleasantness of a stressful or painful stimulus
    4. Increase catecholamine release in response to a stressful stimulus

F. Opioid analgesia.

Systemic delivery of opioids yields a selective reduction in an animal's response to a noxious (painful) stimulus. These effects on pain behavior have two psychophysical components:
1) Increases stimulus intensity required to induce a pain report (i.e., raises pain threshold).
2) Serves to alleviate anxiety.

Each receptor class has been shown to be associated with altered pain states as defined by:
•   The ability of the respective agonists to produce analgesia (e.g., morphine, DPDPE, butorphanol).
•   Antagonism of the analgesia by naloxone and respective receptor selective antagonists (see Table 1).
•   Changes in response to a given agonist in animals deprived of the respective receptor protein (knock-out mice, antisense treatment).

While all classes of opioids have some activity as analgesics, the most efficacious and the most widely used clinically are those that act upon the μ opioid receptor (see Table 1).

1. Site of analgesic action of μ opioids.
    Where in the organism do opioids act to alter pain transmission?
    •   Direct injection of opioids into the brain using chronically implanted microinjection guides in nonanesthetized animals shows that opioid receptors modulating pain behavior are found in several restricted brain regions.

- Brain regions where a local action of opioids produce an analgesic action: amygdala, substantia nigra, periaqueductal gray area (PAG), rostroventral medulla (RVM), and spinal cord (Figure 7).

Figure 7. Sites of opioid analgesic activity in the rat brain.

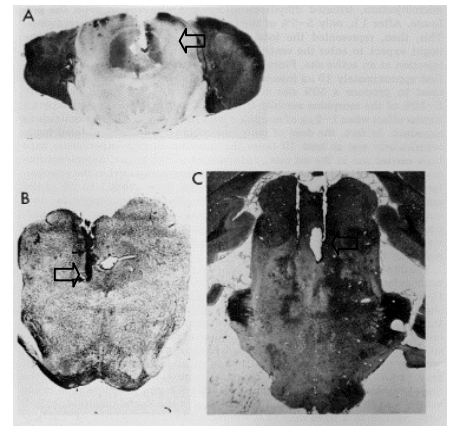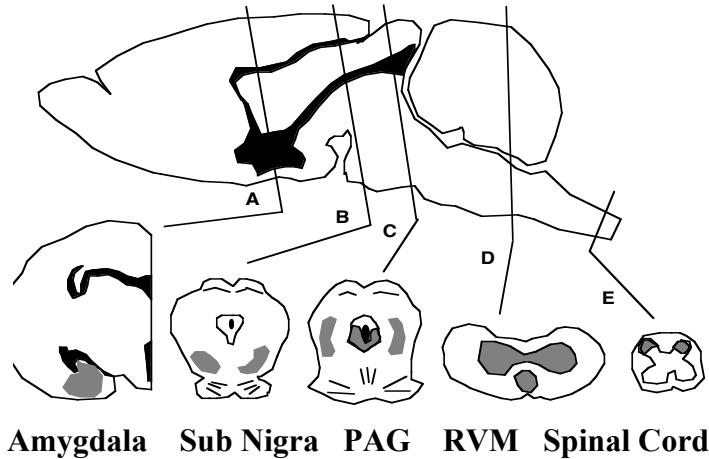**Amygdala   Sub Nigra   PAG   RVM   Spinal Cord**

Figure 8. Active sites (arrow) for morphine in the PAG of A, mouse; B, rat; and C, primate.

- Effects of intracerebrally-delivered agents display appropriate opioid receptor pharmacology and are reversed by naloxone, emphasizing an effect mediated by an opioid receptor in that brain region.

2. Supraspinal mechanisms of opioid analgesia.
    - Best characterization of the opioid receptor sites mediating analgesia is the mesenephalic periaqueductal gray area (PAG) (Figure 8).
    - Microinjections of morphine into PAG blocks nociceptive responses in a naloxone-reversible fashion in mouse, rat, rabbit, cat, dog, and primate.
    - Local effect serves to block not only spinally-mediated reflexes (such as the tail flick) but also supraspinally-organized responses.
    - Within the PAG, μ opioid binding appears to be on local interneurons.
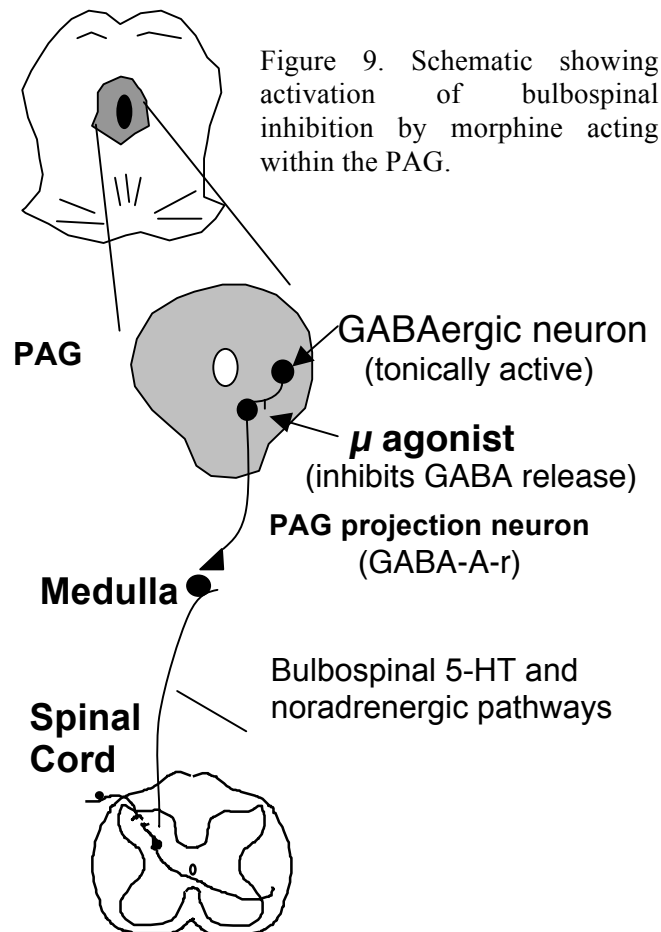

Figure 9. Schematic showing activation of bulbospinal inhibition by morphine acting within the PAG.

PAG

GABAergic neuron (tonically active)

***μ* agonist** (inhibits GABA release)

PAG projection neuron (GABA-A-r)

Medulla

Spinal Cord

Bulbospinal 5-HT and noradrenergic pathways

- The following mechanisms are hypothesized for opioid actions within the PAG (Figure 9):
  1) Opioid actions block the release of GABA from tonically active interneurons in the PAG that otherwise inhibit excitatory projections to the medulla.
  2) PAG projections to the medulla serve to activate bulbospinal projections releasing 5-HT and/or NE at the spinal level.
  3) At the spinal level, NE and 5-HT, acting though α_2 adrenergic and 5-HT receptors, respectively, serve to locally inhibit spinal pain input.
- In addition to the activation of descending pathways, there are other mechanisms that have been implicated, including activation of ascending 5-HT/NE pathways to fore brain centers regulating emotionality. These mechanisms are less well characterized.

3. Spinal action.
   - A local action of opioids in the spinal cord selectively depresses discharge of spinal dorsal horn neurons activated by small (high threshold) but not large (low threshold) afferents.
   - Intrathecal opioids attenuate the response to stimulation of sensory afferents and produce a potent, naloxone-reversible analgesia.
   - Mechanisms of this selective spinal inhibition:
     1) Opioid receptors are present in the substantia gelatinosa (region of spinal cord where small sensory afferents [C fibers] activated by tissue injury terminate).
     2) Opioid binding is present on the terminals of C fibers and post-synaptically on second-order neurons (Figure 10).
     3) Opioids reduce release of small primary afferent peptide transmitters (substance P). Block of release results from block of primary afferent voltage-gated Ca^{2+} channels (Figure 10).
     4) A post-synaptic action is demonstrated by ability to block excitation of dorsal horn neurons evoked by glutamate. This post-synaptic action reflects an increase in pK leading to membrane hyperpolarization (Figure 10).

Figure 10. Dorsal horn opioid action.

     5) Joint ability of spinal opioids to reduce release of excitatory neurotransmitters from C-fibers as well as decrease excitability of dorsal horn neurons accounts for powerful and selective effect upon spinal pain processing.
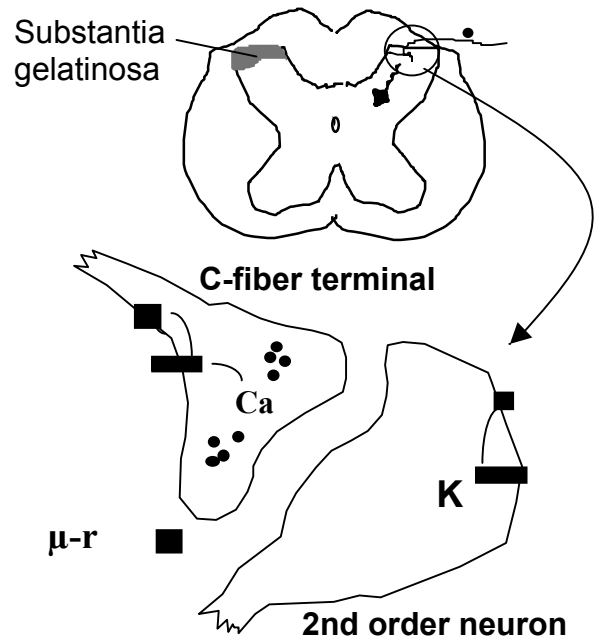
G. Non-analgesic effects mediated by opioid receptors.

Aside from analgesia, opioids produce a constellation of effects that reflect upon the association of the respective receptor with a variety of central and peripheral systems.

1. Sedation: μ and ∂ receptors.
   Agonists reduce arousal and promote sedation.
   • Effect mediated by inhibition of ascending excitatory drive from the mesencephalic reticular activating systems at the brain stem level.

   Clinical relevance
   • Sedative effects potentiated by sleep, other depressants.
   • Opioids are used to induce sedation and augment anesthetic state in surgery.

2. Respiration: μ receptors.
   μ opioids reduce response to CO_2
   • Effect is secondary to depression of brainstem responsiveness to CO_2 (Figure 11).

   Clinical relevance
   • Agonists reduce the respiratory drive evoked by a decrease in the partial pressure of CO_2. The resulting depression of respiratory rate and effort can lead to potentially fatal apnea.

Figure 11: Effect of inspired CO_2 on respiratory rate. Morphine shifts the curve downwards and reduces its slope.

   • Opioids reduce "air hunger" (dyspnea) in patients suffering from respiratory or cardiovascular insufficiency or from cancer.
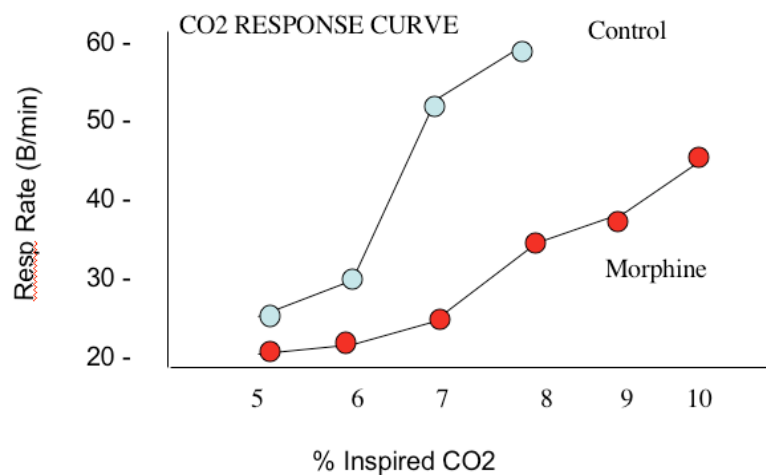
3. Gastrointestinal function: μ and ∂ receptors.
   Agonists have multiple effects:
   • Reduce biliary, pancreatic, and intestinal secretions.
   • Increase resting tone in the small and large intestine, leading to an increase in non-propulsive contractions (bowel spasm).
   • Net effect is to slow passage of intestinal contents, increase their viscosity, and induce constipation.
   • Effect is mediated in part by an inhibition of the release of acetylcholine in the myenteric plexus.
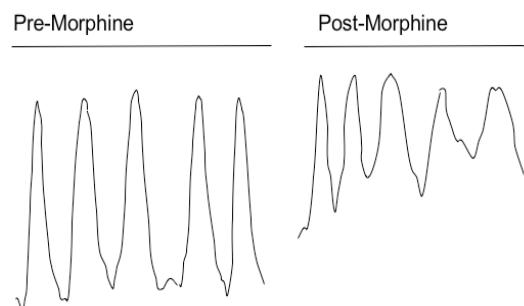

Figure 12. Spontaneous gut motility prior to and after morphine. Note increased basal tone.

- Increased biliary tract tone can lead to spasm and induce colic.
- Action can be produced by direct peripheral effect of opioid on GI tract:

Clinical relevance

- Management of diarrhea by peripherally acting oral opioid anti-diarrheal medications such as *loperamide* [Imodium®], which do *not* enter the brain to a significant extent at therapeutic doses.
- Constipation is an important side effect of even therapeutic doses of opioids. In some patients, this can be treated by a peripherally-acting opioid antagonist such as *methylnaltrexone* [Relistor®].

4. Emesis: μ, ∂, κ receptors.
   - Agonists act at opioid receptors in the chemoemetic trigger zone in the dorsal brainstem (area postrema).

   Clinical significance
   - Agonists may induce nausea and emesis at post-operative and analgesic doses. More common in ambulatory patients, suggesting a vestibular component.

Figure 13. Primary sites of action of opioids in the induction of emesis.

5. Rewarding properties : μ receptors.
   Agonists can have very strong rewarding actions.
   - Behavioral and pharmacological data point to a pivotal role of mesocorticolimbic (MCL) dopamine system, a basal forebrain circuit implicated in reward and motivation
   - Mesolimbic dopamine system originates in ventral segmental area (VTA) and projects to nucleus accumbens (NAc) in forebrain. Opioid receptors in NAc *inhibit* local inhibitory (GABAergic) interneurons regulating activity of local
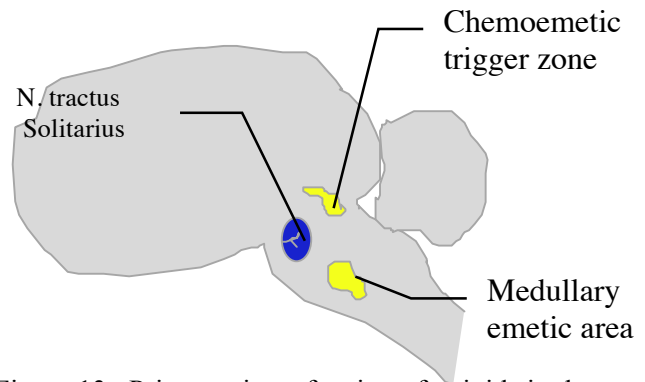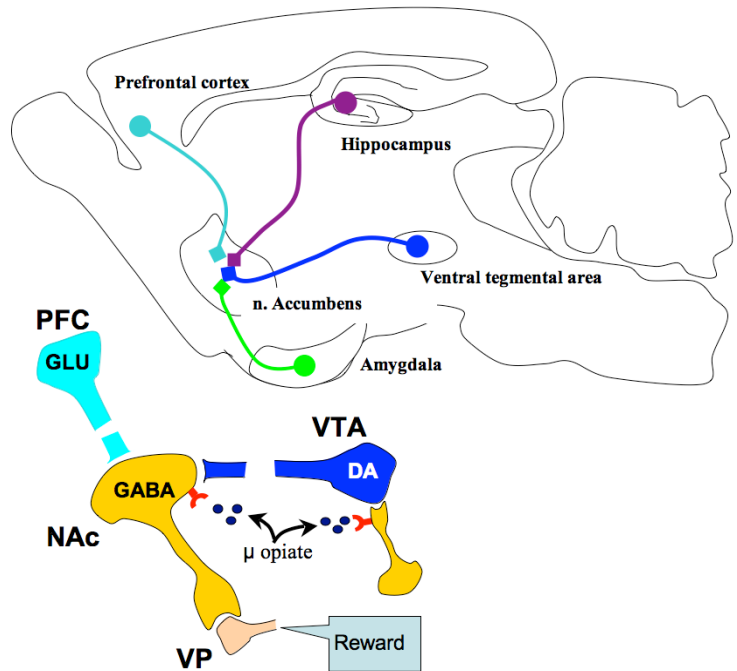

Figure 14. Saggital schematic of rat brain displaying dopaminergic and glutamatergic inputs from several regions including the Ventral tegmental area (VTA) and Prefrontal cortex (PFC), respectively into the n accumbens (NAc). Opiate inhibition in VTA on gabaergic interneurons or in the NAc, increase dopamine outflow from the ventral pallidum (VP)

(nucleus accumbens) mesolimbic dopamine-releasing terminals.
- *Increased* dopamine release is positively reinforcing.
- Opioids with rapid onset of action, because of rapid movement into the brain, have higher rewarding properties (e.g., lipid soluble agents such as heroin = 3,6 diacetyl morphine, which is deacetylated to morphine after entering the brain).

Clinical significance.
- Rewarding properties are considered to underlie the abuse/addition potential associated with many μ opioids.
- Rewarding properties contibute to the potential risk of μ opioids for drug diversion.

6. Miosis: μ receptors.
Opioids induce pupillary constriction (miosis).
- Results from net excitation of parasympathetic nerves that innervate the pupil, leading to contraction of the pupillae sphincter (constrictor) muscle.
- Opioids block the activity of inhibitory interneurons (GABAergic), resulting in increased parasympathetic outflow and miosis.

Clinical significance
- Miosis is an important sign of opioid intoxication.
- Does *not* show tolerance.

Figure 15. Mechanism whereby opiate with an action in the brainstem cause an increase in parasympathetic outflow and miosis.

7. Cardiovascular: μ receptors.
High doses of opioids are typically well tolerated from a cardiovascular perspective.
- Opioids cause increased excitation of parasympathetic nerves that innervate the heart (vagus), leading to an atropine-sensitive decrease in heart rate (Figure 16).
- Morphine can release histamine from mast cells (unlike agents such as fentanyl) and can produce significant peripheral vasodilation and hypotension by that mechanism.
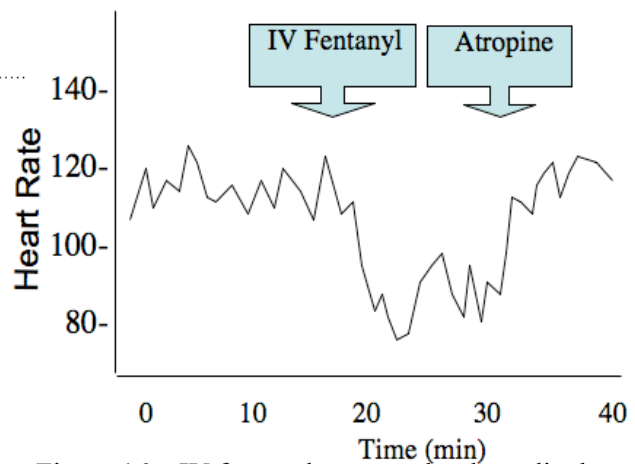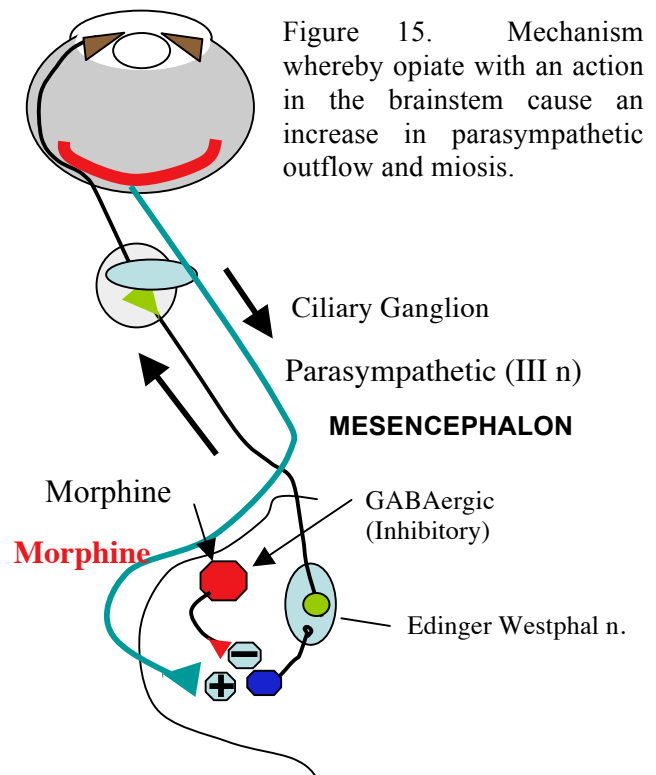
Clinical significance

Figure 16. IV fentanyl causes a bradycardia that is reversed by atropine, indicating a vagotonic effect of μ opioids.

- Opioids are widely used as induction agents in cardiac surgery (fentanyl).
- Bradycardia is common, leading to pretreatment with a muscarinic antagonist such as atropine.

8. Neuroendocrine: μ and κ receptors.
   Opioids have broad effects upon the hypothalamic-pituitary axis. Some of these effects are due to a direct action upon the releasing terminals, while others involve the inhibition of interneurons such as those releasing dopamine. Several important one are listed below.
   - μ Opioid agonists inhibit hypothalamic terminal release of gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF).
   - Conversely, μ opioids increase prolactin secretion by reducing local release of dopamine, which inhibits prolactin secretion.
   - κ Opioid agonists by an action on antidiuretic hormone (ADH) releasing terminals in the posterior pituitary inhibit secretion; and, thereby increase urine flow rate. μ agonists may indirectly stimulate ADH secretion (secondary to hypotension produced by mast cell degraulation) and thereby decrease urine flow.

   Clinical significance.
   - While the pituitary hormone effects do not present a clinical problem acutely, with chronic delivery (as in methadone maintenance) they can be result in signs of hypopituitarism.

Figure 17. Schematic showing opioid action in the hypothalamus and posterior pituitary in altering the release of several hypothalamic-pituitary hormones.
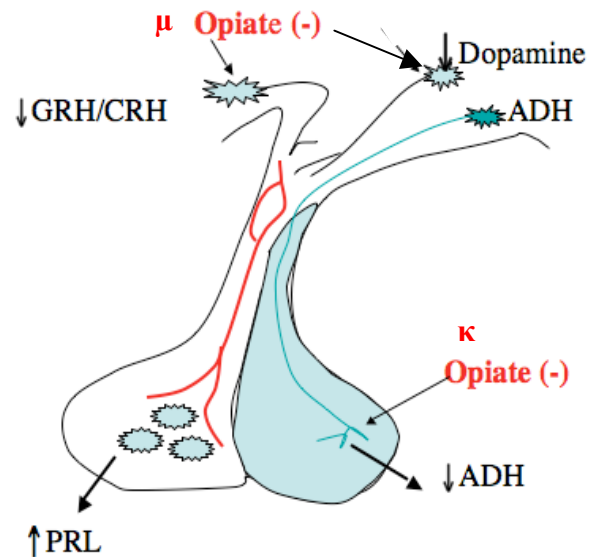
H. Clinical use of opioids as analgesics.

1. Pain possesses two dimensions:
   1) **Sensory-discriminative component**. The quantifiable sensation that relates to the sensory input ("I hurt here, on a scale of 1 to 10, 6").
   2) **Affective-motivational component**. Relates to the emotional context of the pain, e.g., suffering.

2. Pain may arise from three principal types of stimulation conditions, which reflect the contribution of specific underlying mechanisms:

1) Acute stimulus. Acute activation of small high-threshold sensory afferents (A∂ and C fibers) generates transient input into the spinal cord, which in turn leads to activation of neurons that project contralaterally to the thalamus and thence to the somatosensory cortex. A parallel spinofugal projection is to the medial thalamus and from there to the anterior cingulate cortex, part of the limbic system. The output produced by acutely activating this ascending system is sufficient to evoke pain reports.
   Examples: hot coffee cup; needle stick, incision.

ii) Tissue injury. Tissue injury results in local release of active chemicals (e.g., bradykinin, prostanoids, potassium) that initiate persistent activation of small sensory afferents. Persistent input causes activation of the ascending pain pathways and leads to a "spinal sensitization." This spinal sensitization predictably alters the content of the message arising from a sensory stimulus to yield an exaggerated output in response to a given small afferent input, e.g., **hyperalgesia**.
   Examples: burn, post-incision, abrasion of the skin, local inflammation, musculoskeletal.

3) Nerve injury. Injury to the peripheral nerve yields complex anatomical and biochemical changes in the nerve and spinal cord that induce spontaneous **dysesthesias** (shooting, burning pain) and **allodynia** (light touch hurts). This nerve injury pain state may not depend upon the activation of small afferents, but may be initiated by low threshold afferents (e.g., Aß fibers).
   Examples: nerve trauma, diabetic neuropathy, post-herpetic neuralgia.

In each case, it is believed that the input relating to the sensory discriminative dimension likely travels over the specific somatosensory pathways reaching the somatosensory cortex. The affective motivational component appears to tap into the brain centers that reach areas of the limbic forebrain (e.g., anterior cingulate gyrus) that appear to underlie aspects of emotionality (Figure 19).

The distinction between mechanisms is important as it reflects upon the types of medications that might be expected to be effective in a given pain state.

I. Analgesics: general principles governing use.

1. Prevalence of pain.
   a) Cancer (CA): 30% to 50% of CA patients experience pain with treatment; 70% to 90% of people with advanced CA experience pain.
   b) Back pain: at any given time, about 1% of US population is chronically disabled due to back problems.
   c) Osteoarthritis: most frequent cause of disability, 20 million today in the US.

2. Rationale for pain management

a) Physiological impact of stress and behavioral suppression produced by pain.

    i)   Reduced mobility → Deconditioning, muscle wasting, joint stiffening, decalification, cutaneous ulcers, lung ateletasis.

    ii)   Autonomic hyperactivity → Blood pressure, heart rate, suppression of gastrointestinal motility, reduced secretion

    iii)   Psychological state → Depression , (helplessness syndrome), anxiety

b) Formal recognition of importance of pain control.
Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Primary accreditation for hospitals, outpatient clinics, nursing homes; accreditation standards:
- Recognize the right to appropriate assessment and management of pain.
- Identify patients with pain, and follow up.
- Educate providers to assure competency.
- Ensure that pain does not interfere with participation in rehabilitation.
- Address patient needs for symptom management in discharge planning.
- Collect data to monitor effectiveness of pain management.

c) The law
California Pain Patients' Bill of Rights (California Senate Bill 402). Authorizes physician to prescribe or administer controlled substances to a person in the course of treating that person for a diagnosed condition called intractable pain,

J. Factors governing analgesic requirements.
1. Pain states are not constant and will vary over time.
    -Time course of post-operative pain (hrs to days).
    -Daily cancer/arthritis flares (Figure 22).
    -Changes in magnitude of pain state during daily routine of a chronic pain patient; ongoing pain versus incident (movement-induced or incident) pain. Need for ongoing management of increased or decreased pain state: altering analgesic dosing use of rescue medications.
2. Pain states may vary by mechanisms (see above).
- Most clinical pain states include a mixture of acute, tissue injury, and nerve injury (neuropathic) components arising from the pathology and its treatment.
- Many pain states have multiple pain sites.
- Consider a cancer pain patient:
  - Multiple sites: 70-90% of CA patients have > 2 pain sites; 40% of CA patients have > 4 pain sites.
  - Multiple mechanisms:
    - Tumor bulk leads to skin erosion, bone erosion (tissue injury), and nerve compression (neuropathic pain).
    - Radiation and chemotherapy lead to nerve injury

- Patient movement may produce an acute pain stimulus (incident pain). Break through and/or incident pain seen in >50 -70% of patients.

HOURLY PEAK PAIN SCORES
68-year-old male. Prostate CA, femoral metastasis

* Toiletry/cares
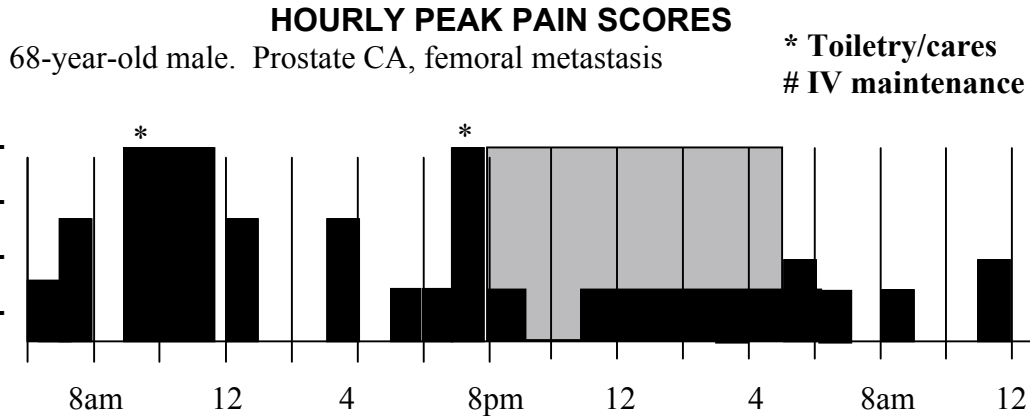**# IV maintenance**

Figure 22. Peak hourly pain scores of cancer patient. Patient is medicated with PO morphine (350 mg/d), ibuprofen (1200 mg/d), steroids, fentanyl patches. Note periods of pain relief interspersed with intervals of severe pain reflecting incident events that arise from daily care and treatment. Gray inset indicates sleep interval interspersed with periods of awakening secondary to pain.

3. Relative efficacy of analgesic classes in modulating different pain states.
Different classes of analgesic compounds modulate different mechanisms and vary in their efficacy in managing different pain states. In general, the following relative efficacies are representative for several classes of agents commonly used in pain management.

Many pain states represent a mixture of mechanisms with one perhaps predominating. Thus, post-operative pain or acute trauma may be primarily tissue injury and inflammation while diabetic neuropathy or post-herpetic neuralgia may be largely nerve injury. With some surgical interventions and chronic injury states (e.g osteoarthritis) it is likely that both tissue and nerve injury are present.

DRUG CLASS	RELATIVE EFFICACY IN PAIN STATES
NSAIDs (cyclooygenase inhibitors) (*ibuprofen*, *aspirin, acetominophen**)	Tissue injury >> acute stimuli = nerve injury = 0
Opioids (μ agonists) (morphine, hydromorphone)	Tissue injury = acute stimuli ≥ nerve injury > 0
Anticonvulsants (*gabapentin*, *topiramate*)	Nerve injury > tissue injury = acute stimuli = 0
Antidepressants (*amitryptiline*, *duloxetine*)	Nerve injury ≥ tissue injury >> acute stimuli = 0
* Mechanism not certain, not likely COX inhibition**.**	

4.   Analgesic drug selection (opioids).
• Duration of pain state
Chronic (arthritis, CA) vs. transient (burn, post-operative)

• Routes available

Acute treatments: IM, IV, buccal, and spinal.
Chronic treatments: PO (slow release formulations of morphine), skin patch (fentanyl), intrathecal (catheter).

• Specific indications or contraindications of drug, e.g., altered liver function

• Intensity of pain state
Mild (sunburn, mild abrasion) vs. severe (post-operative, post-arthroscopy, severe joint disease).

5. Role of pain intensity in drug selection.
• Opioids can diminish a pain state in a dose-dependent fashion; as the intensity of the stimulus rises (mild to severe), the dose-response curve for the agonist (e.g., morphine or fentanyl) shifts to the right (Figure 23).

• With mild pain, opioid drugs with limited intrinsic activity (partial agonists such as buprenorphine) may be fully effective.

• As pain increases, partial agonists may fail to have sufficient intrinsic activity to produce a maximum pain relief equivalent to a full agonist, and their dose-response curves will display a plateau (Figure 23).

• Graded analgesic therapy (World Health Organization ladder; Figure 24).
  -Weak to strong opioids
-Combination analgesic therapy (NSAIDs + opioids)
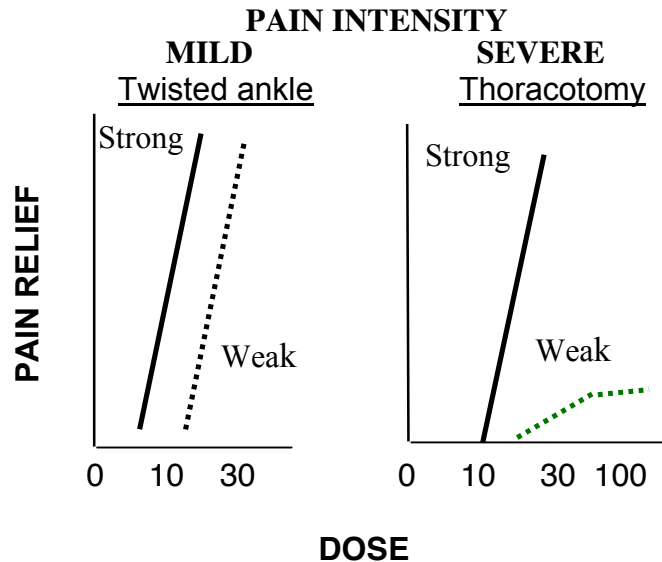-Adjuvants to manage side effects.

Figure 23. The ability of strong and weak opioid agonists (e.g., morphine and bupenorphine, respectively) to block mild pain (*left*). In contrast, a more intense pain (*right*) requires a higher dose of the strong agonist, and the weaker agonist behaves as a partial agonist.

Figure 24. World Health Organization (WHO) Ladder.

SEVERE PAIN
NSAIDs
"Strong" opioids
Anticonvulsants
Adjuvants
   Laxatives
   Antiemetics
   Stimulants
   Antidepressants

MODERATE PAIN

NSAIDs
"Weak" opioids

MILD PAIN
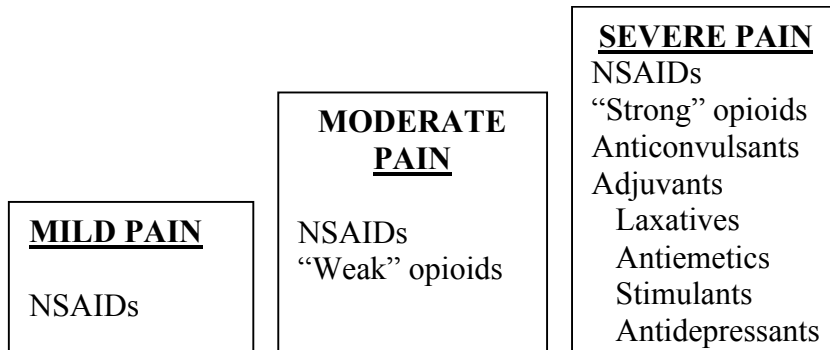
NSAIDs

- Combination analgesic therapy is common in severe chronic pain states; typical CA patient may be on 3 to 4 pain medications concurrently.

- Note combination therapy is based on:
  1) Drugs with non-overlapping mechanistic profiles (e.g., NSAIDs and opioids).
  2) Partial agonists and full agonists are not mixed, because "weak antagonizes strong."

8. Routes of opioid delivery for pain control.
   Strategy is common sense: always try to employ the least invasive, most convenient, lowest side effect profile. For chronic conditions, look for the least frequent dosing interval.
   - PO (slow release formulation of morphine, hydrocodone, and methadone): chronic pain
   - Mucosal absorption; oralets absorbed though buccal mucosa (fentanyl). Rapid absorption. Used for incident (breakthrough) pain.

   - IM (meperidine): acute incident pain.

   - Skin patch (transdermal) (fentanyl): patch long-term (24-48 hrs) (Figure 25).

   - IV (morphine, fentanyl): used for acute pain control, also in conjunction with an external pump that can be controlled (within limits) by the patient (**PCA = patient-controlled analgesia**; Figure 26).

Figure 25. Fentanyl patch   Figure 26. PCA pump.

   - Epidural/intrathecal (morphine, fentanyl): bolus or continuous infusion. Bolus delivery 8-24 hrs; continuous infusion by subcutaneously implanted pump.

9. Clinical examples of analgesic therapeutic regimens.
    As noted, many clinical pain states are considered to represent a mix of mechanisms, with one perhaps predominating. This emphasizes that certain "multi-modal" therapies may be required.

SEVERITY OF PAIN	ACUTE Post-operative Burn	CHRONIC Arthritis Back pain Cancer
MILD-MODERATE	NSAID – PO NSAID + codeine - PO	NSAID - PO NSAID + codeine - PO

MODERATE –SEVERE	PCA – IV
	Buprenorphine - IM
	Morphine - bolus epidural
	NSAID - PO
	
	Rescue medication:
	IV PCA , fentanyl patch
		Morphine - PO
		NSAID - PO
		Intrathecal opioid infusion
		
		Rescue medication:
		  IV PCA, fentanyl patch
		
		Adjuvant analgesics:
		  Anticonvulsants
		  Local anesthetics
		
		Adjuvants for side effects:
		  Emesis
		  Constipation
		  Depression

K. Tolerance/dependence and addiction.

1. Tolerance.
    a. Reduction in effect over time associated with the repeated delivery of an opioid agonist, or an increase in the dose required to yield an equivalent response after successive doses of the opioid.
    b. Tolerance can be extreme. For example, 10 mg PO in a naïve individual is a high dose versus 100s of mg IV in a severely tolerant individual (which may produce only minor sedation).

    c. On the other hand, under stable conditions, opioid dosing can be remarkably stable. In one study of
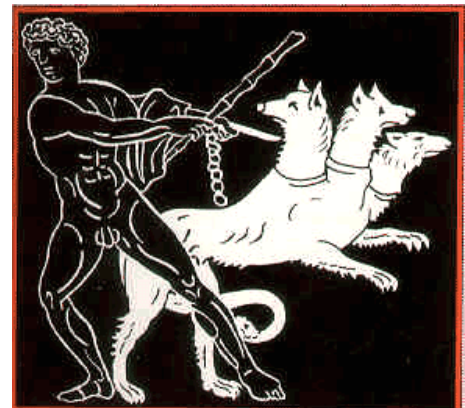
1000 advanced CA patients, only 5% required an average daily dose increase of more than 10%.

d. Still, tolerance exists and the rate of tolerance development to an opioid can differ with the endpoint. Thus:

    Most rapid ....Less rapid………..........Not at all
    <u>Euphoria > sedation > analgesia > nausea >constipation > miosis.</u>

e. Loss of an analgesic response in a chronic pain patient could be secondary to:
    o Pharmacokinetic tolerance: Increased metabolism or clearance….unlikely
    o Pharmacodynamic tolerance: Reduced receptor number or loss of second messenger coupling. Contribution of pharmacodynamic mechanism to loss of effect in clinical analgesic therapy is controversial.
    o Increased pain: As an injury state evolves, the pain stimulus can become stronger. In that case, the dose of analgesic required to produce a desired degree of pain relief will rise.
    o Development of non-opioid sensitive pain Opioids are most effective in managing pain observed following tissue injury (post-operative/burn/inflammation) but are <u>less</u> effective in controlling pain that arises from nerve injury (neuropathic pain). As a tumor progresses, it may impinge upon nerves and initiate a neuropathic pain state. Multiple sclerosis may yield spinal and nerve injuries leading to neuropathic pain states. These states may have an opioid-refractory component.
    o Suffering vs. pain Opioids block nociceptive transmission. The pain of the patient may possess components of duress that reflect upon the emotional and cognitive responses of the patient to the pain state. Removal of the stimulus may be necessary but not sufficient to control the suffering.

2. Dependence.
  a. State of adaptation manifested by drug class-specific withdrawal syndrome produced by abrupt cessation (e.g., by drug abstinence) and/or administration of an antagonist (e.g., naloxone).
      b. Withdrawal characterized by exaggerated appearance of physiological signs that are suppressed by opioid agonists.
      c. Typical signs are agitation, diarrhea, hyperalgesia

3. Addiction.
    • Drug seeking behavior motivated by strong efforts to acquire drug for non-therapeutic self-administration.
       o Frequently defined in terms of the rewarding properties of the drug.
    • Characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and reported craving.
       o Aberrant behaviors such as selling prescription drugs, prescription forgery, stealing drugs from others, and obtaining prescription drugs from nonmedical sources are clear indicators of an addiction disorder.

- Pseudo-addiction may occur in the setting of continuous pain when inadequate doses are utilized and/or excessive dosing intervals are employed.
- Management of addiction has several focuses: control of drug seeking behavior and control of withdrawal (manifestation of dependence).
- Approved for the treatment of opioid addiction by preventing symptoms of withdrawal from heroin and actions of other opioids:
  - Methadone maintenance
  - Buprenorphine hydrochloride [Subutex®] or buprenorphine hydrochloride + naloxone hydrochloride [Suboxone®].

N. Ethical issues in opioid use.

1. Physician responsibility: pain legislation in California.
   - Patient's bill of rights: series of legislative initiatives in California (since 1990) giving statutory recognition of patient's right to receive adequate medical pain management.
   - Tamper-resistant security forms.
   - Responsibility for diagnosis and appropriate care.

2. Opioid addiction and therapeutic opioid exposure: is there a reason to withhold therapeutic use of opioids for fear of addiction?
   - Tolerance and dependence may occur with chronic opioid therapy, but incidence of "addiction" in patient medically treated is controversial.
   - Abuse is a real concern.
   - Physician has the responsibility to use due care in prescribing opioids.
     - Maintain oversight of patient, be alert to signs of abuse
     - Patient contracts.
     - Signs of aberrant drug use.
   - Drug diversion is a growing problem
     Example: Introduction of OxyContin® in 2000 resulted in increasing patterns of abuse ("hillbilly heroin"). Unlike Percocet® (oxycodone plus acetaminophen), for which the potential for abuse is limited by the presence of acetaminophen, OxyContin® contains only oxycodone and inert filler. Abusers crush tablets to defeat the sustained-release mechanism and snort or inject the resulting powder to achieve rapid absorption into the bloodstream. It was once felt that "combination" opioids (those that contain one or more additional, non-narcotic ingredients) would be less subject to abuse, since, for example, the amount of acetaminophen present in large overdoses of Percocet® would cause gastric upset and liver damage. However, it has been demonstrated that abusers seeking the euphoric "high" are not deterred by gastrointestinal symptoms.

3. Use of opioids in chronic non-terminal pain.
   - Controversial because of perceived risks of addiction and societal stigma related to opioid use. Nevertheless, there is an increased prevalence of opioid use in chronic pain patients (e.g., back pain, arthritis) because of demonstrated efficacy and improved quality of life.

- Use of opioids in this venue requires contractual agreements with patients to comply with medication instructions, no doctor shopping, and no diversion.

4. Use of high-dose opioids in terminal patients where dosages may lead to morbidity.

- In late-stage diseases with intense pain, opioid dosing necessary to achieve pain relief may lead to significant sedation and decreased respiratory function. Such a condition may result in death.

- Very complex ethical and societal issues are at play. Nevertheless, in terms of palliative care, it is appreciated that the aim is to give opioids in the doses required to render the patient comfortable, not with the intent to induce demise.

PAIN MANAGEMENT IMPERATIVE

Prevalence of pain….high
> **Cancer:** 30%- 50% experience pain with treatment; 70%- 90% with adv CA experience pain.
> **Back pain:** at any given time, 1% of the US population is chronically disabled due to back problems
> **Osteoarthritis:** most frequent cause of disability, 20 million today.
> **Common problem:** 65% of patients in physicians' offices are there due to a pain complaint.

Adequate management is the standard of care.

Failure to manage has significant costs and consequences.

CURE WHEN POSSIBLE ….PALLIATE ALWAYS!