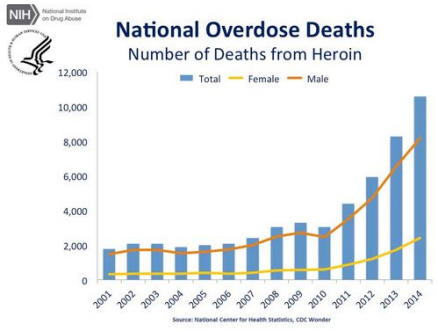
# Narcotic Analgesics I

*Blanton*

**SLIDE 1:**

*We will be spending the next 90 minutes discussing narcotic analgesics- that is morphine, oxycodone, heroin, etc. These drugs act primarily thru the opiate receptor system. I always like to begin by presenting two factoids that I believe illustrate the power of this system: (1) Ok imagine you are in pain! Now I tell you that I am going to give you an injection of morphine or heroin. Even if I instead give you an injection of just saline- 50% of you will report that your pain is significantly reduced- that is quite a placebo effect. However, if instead of saline I give you an injection of Naloxone, an opiate receptor antagonist- the placebo effect is eliminated. In other words you are activating your opiate receptor system to induce analgesia. (2) acupuncture can be used to reduce pain. However, Naloxone will block this effect- in otherwords the acupuncture is activating your opiate receptor system.*

**SLIDE 1A**: *The use of narcotic analgesics for effective pain management has certainly had its flip side……. With prescription narcotic analgesics helping to fuel the current heroin epidemic….*




**Back to SLIDE 1:** So narcotic analgesics. The name narcotic is somewhat misleading, because it implies narcosis or somnolence. The name opiate or opioid is more precise because it connotes analgesia, without causing sleep or loss of consciousness.

**SLIDE 2:**

The terms opiate or opioid, as you are probably aware, refers to opium, the crude extract of the Poppy plant, *Papaver somniferum*. Opium comes from the seed pod of the plant after the petals have dropped. Some 20 or more alkaloids are present in opium, including morphine, codeine, and thebaine.

Opium has been in use for many centuries. The first verifiable written documentation of its use was in 300 BC. Morphine was first extracted from opium and its potent properties were observed by the German pharmacist, Serturner, in the early 1800s. He named the extract morphine, after the Greek god of dreams, Morpheus.

**SLIDE 3:**

Historically, the opiates have been used for many medical problems. They have been used as analgesics, as preanesthetic medications, as anesthetics, as spinal analgesics, as well as for pulmonary edema, cough, and diarrhea.
Indeed early on opiates were used in the control of dysenteries. Certainly opiates have been used as sedatives. You may have read about laudanum, the popular sedative in the 1800s- laudanum is a alcohol mixture (tincture) of opium. (Recreation) Abuse potential of opiates are well known- in various forms these drugs have been smoked, snorted, ingested, and injected.

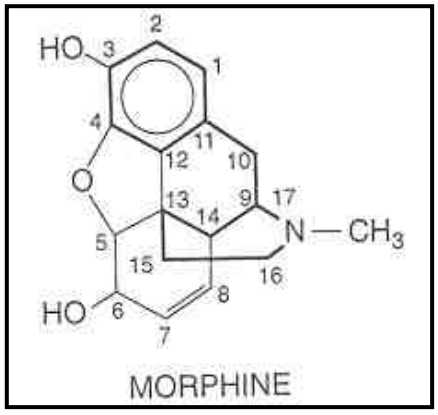
**SLIDE 4:**

Opioid compounds can be broken down into 3 main categories:

1) The naturally occurring extracts of opium such as morphine and codeine, which are agonists;
2) The synthetic opioids, which may be divided into 3 subsets: the ***agonists,*** which have a similar pharmacological profile with that of morphine, the ***antagonists,*** which block the actions of opiates, and the ***mixed agonists/antagonists***, which simultaneously have stimulatory actions at one or more subsets of opiate receptors and inhibitory actions at one or more subsets of opiate receptors.
3) The third category is the endogenous peptides, or opiopeptins, which include endorphins, enkephalins, and the dynorphins.

**SLIDE 5:**

Morphine is the prototypical opiate.
Its structure is shown here.



MORPHINE

Many of the derivatives of morphine are simple substitutions. For agonists, the substitutions are typically at the 3 or 6 positions and sometimes at the 17 position.
For instance:

Codeine has a methoxy substituent at the 3 position, which makes it a weaker agonist that morphine.
Hydromorphone has a carbonyl group at position 6 instead of a hydroxyl; this substitution makes it fairly equivalent to morphine with respect to efficacy.
Heroin, contains an acetyl group at both the 3 and 6 positions. Heroin crosses the blood/brain more quickly than morphine, but it is quickly metabolized to 6-monoacetylmorphine and morphine in nervous tissues,
***-Heroin itself is not pharmacologically active it these metabolites that are responsible for heroin's effects.***

The mixed agonist/antagonists or pure antagonists typically have substitutions at the 17 position. This tertiary amine is modified, usually with a bulkier alkyl group.

**SLIDE 6:**
Several receptors for opiates have been identified in the CNS. These are the mu, kappa, delta, and sigma receptors. Multiple subtypes exist for the mu and kappa receptors.

The mu receptor is responsible for spinal and supraspinal analgesia, respiratory depression, miosis, euphoria, reduced GI motility, and physical dependence. Most of the agonists, such as morphine, that are used interact selectively with mu receptors at standard dosages. It is important to note that at higher doses, morphine and other agonists lose their selectivity and interact with the other receptors.

The kappa receptor is responsible for spinal and to a lesser extent supraspinal analgesia. The kappa receptor also produces respiratory depression and miosis. In contrast with the mu receptor, the kappa receptor produces dysphoria. The delta receptor produces both spinal and supraspinal analgesia, but spinal analgesia is more robust.

The N/OFQ /sigma receptor may or may not be a true opiate receptor. It appears to be associated with dysphoria and hallucinations and may be a site of action for PCP.

**SLIDE 7:**
The opiate receptors are coupled to G proteins. Activation of these receptors results in the inhibition of adenyl cyclase and subsequent reduction in the amount of cAMP formed.
Postsynaptically: the effect is to enhance K+ channel current which results in hyperpolarization of the neuron. For pain transmission…decrease pain perception!

**SLIDE 8:**
Presynaptically: Opiate receptor activation leads to inhibition of voltage-gated Ca channels and suppression of the release of neurotransmitters such as NE, DA, 5-HT, Ach, and Substance P is blocked.

Therefore, Opiate actions are thought to be through (1) inhibition of postsynaptic signaling and (2) the suppression of transmitter release.

**SLIDE 9:**
The opiate receptors are modulated by endogenous compounds. The endogenous opiates represent 3 distinct classes of peptides. The endorphins are derived from proopiomelanocortin. The enkephalins are derived from proenkephalin A, and the dynorphins are derived from proenkephalin B.

**SLIDE 10:**
Endorphins (POMC) are fairly restricted in the CNS. Precursors are found in areas of the brain where electrical stimulation can reduce pain. High levels are found in the arcuate nucleus which projects broadly in the brainstem and limbic areas and the spinal cord.
-Peptides from POMC are also found in the pituitary and in islet cells of the pancreas.

Precursors of enkephalins and dynorphins are widely distributed throughout the CNS and are often found together. Proenkephalin peptides are present in the areas of the CNS that are involved in pain perception. For instance, laminae I and II of the spinal cord, the spinal trigeminal nucleus, and the periaqueductal gray area. They are also present in areas that modulate affective behavior, motor control, and autonomic function. Interestingly, they are also found in nerve plexuses, the adrenal medulla, and exocrine glands of the stomach and intestine.

**SLIDE 11:**
It is important to note that not all tissues that have a given precursor peptide have the same peptide products. Differential processing that can be tissue specific results in the presence of different peptide products.

**SLIDE 12:**
Let's consider the CNS effects of opiates. An appropriate place to begin is with **Analgesia**. Pain is an extremely complex effect. An individual's experience with pain can be broken down into 2 basic parts:

1) The original painful sensation and 2) his myriad reactions to it.

Opiate agonists can alter the perception of pain and the reaction to pain. That is, opiates may reduce or eliminate the painful sensation. They may also alter the reaction to pain in that the patient feels relief with less anxiety. Some patients report that they are still aware of the painful sensation but that it doesn't bother them anymore. Opiate agonists may also increase the threshold to pain.

Interestingly, nociceptive pain is usually more responsive to opiates- that is where painful stimuli from injured tissue is transmitted through intact neural pathways. Less responsive to opiates is neuropathic pain which is a result of damage to neural pathways. *Chronic pain affects an estimated 100 million in U.S. at a projected annual cost of $600 billion.*

**SLIDE 13:**
Dull pain is more effectively controlled with opiates than is sharp pain, but sharp pain can be treated effectively, too. Severe pain can usually be effectively treated or at least reduced with proper monitoring and adjustments of the regimen. A person in pain may or may not experience sedative effects when taking opiates. Likewise, changes in mood and cognitive function are variable with opiate administration. If a person is not in pain and takes an opiate agonist, he will experience more unpleasant side effects. Commonly, nausea and vomiting, dysphoria, apathy, and decreases in mentation occur. The existence of pain appears to alter the production or intensity of these side effects.

**SLIDE 14:**
Both **spinal** and **supraspinal** sites have been identified as playing a role in opiate analgesia (mu and kappa receptors).

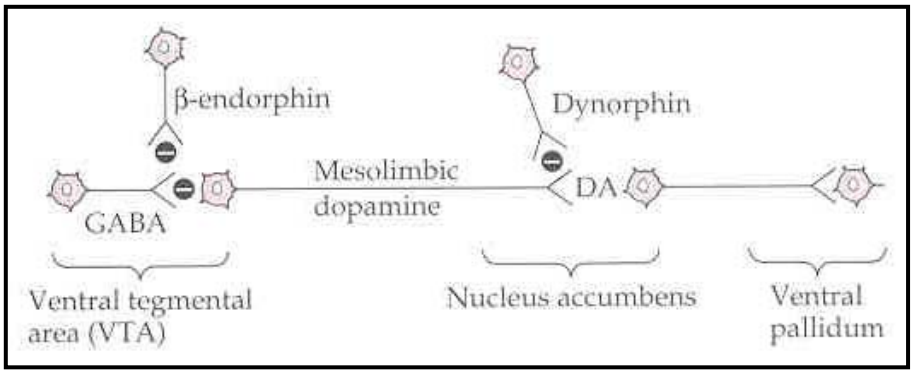
(**Ascending pain pathway-spinothalamic tract**) Nociceptive reflexes are inhibited and profound analgesia is produced when opiates are administered intrathecally (spinal cord) or instilled locally in the dorsal horn of the spinal cord. In afferent fibers, presynaptic localization of opiate receptors inhibits the release of neurotransmitters involved in pain transmission. Furthermore, activation of postsynaptic opiate receptors on interneurons and output neurons of the spinothalamaic tract that relay painful stimuli result in reduced transmission to higher brain centers (*opiate receptor activation on postsynaptic membrane results in increased K conductance-hyperpolarization)*

(**Descending pain pathway-bulbospinal tract**) Profound analgesia can also be produced by instillation of morphine into the third ventricle, as well as sites in the midbrain and medulla (periaqueductal gray matter, nucleus raphe magnus, and the locus correleus). This results in enhanced activity in descending aminergic bulbospinal pathways that exert inhibitory effects on the processing of nociceptive information in the spinal cord.*[ more precisely GABAAR tonic inhbibition of descending pathway is turned off]*

Experimentally, there is a synergistic response to the analgesic effects of morphine when it is applied to spinal and supraspinal sites. *This result suggests that administration of an opiate to a patient by oral or IV route produces analgesia through both spinal and supraspinal mechanisms.*

**SLIDE 15:**

The mechanisms through which euphoria and dysphoria are produced is not clear. However, the ventral tegmentum is thought to be involved. DA neurons in the VT are activated by opiates. [More precisely opiate receptor activation turns off the inhibition of DA neurons by GABAnergic neurons]




These DA neurons project to the nucleus accumbens and are thought to produce the euphoric and reinforcing effects of opiates. Mu and delta receptors appear to be involved in the reinforcing effects.

In contrast: Kappa receptors block the firing of DA neurons and this may underlie their **dysphoric** effects. Other neurotransmitters besides DA may be involved in these pathways.

**SLIDE 16:**

CNS Effects: The equilibration of the hypothalamic heat regulatory mechanism is altered, such that temperature usually falls slightly after opiate administration. Opiates have several neuroendocrine actions. In the hypothalamus, opiates inhibit the release of gonadotropin releasing hormone and corticotropin releasing hormone. The result is that LH, FSH, ACTH, and β-endorphin levels fall. Prolaction levels are increased. Opiates acting at the mu receptor have an antidiuretic effect.

**SLIDE 17:**

Miosis occurs because of activation of mu and kappa receptors on parasympathetic nerves innervating the pupil. Toxic doses result in pinpoint pupils. *[mu receptor activation turns off tonic inhibition by GABAAR of parasysmpathetic tone]*

Convulsions are also thought to be due to mu,kappa, and delta receptors. Opiates activate a number of neurons, particularly those in hippocampal pyramidal cells. They may due this through suppression of GABA release from inhibitory interneurons. Fortunately, doses that are in excess of the therapeutic dose (usually very high) are required to produce convulsions.

**SLIDE 18: Not mediated by mu or kappa receptors**

The antitussive effects of opiates are thought to be produced through suppression of the cough center in the medulla. This effect appears to have nothing to do with the effects of opiates on respiration.

Nausea and vomiting occur because opiates stimulate the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla. This effect varies widely among patients. In addition, nausea and vomiting is rather uncommon in recumbent patients. Nausea and vomiting are much more likely to occur in an ambulatory patient. This suggests that a vestibular component is involved.

**SLIDE 19:**

Respiration is depressed by opiates. Depression is concentration dependent and some depression can be seen at low concentrations. Therapeutic concentrations of morphine reduce rate, minute volume, and tidal exchange. However, therapeutic concentrations of opiates rarely produce problems clinically, unless the patient has underlying pulmonary dysfunction. When opiates are combined with other drugs such as general anesthetics, tranquilizers, alcohol, or hypnotics there is a greater risk for significant respiratory depression.

**SLIDE 20:**

The CO2 sensitivity of brainstem respiratory centers is reduced. Suppression of brainstem centers that control rhythmicity of breathing also occurs. Hypoxic stimulation of chemorecptors in the aortic arch and carotid body are intact, so administration of O2 may produce apnea.

Death from morphine poisoning is almost always due to respiratory arrest. Caution should be exercised in prescribing or administering opiates to patients having any condition that produces respiratory problems.

**SLIDE 21:**
Opiates cause histamine release, which causes bronchoconstriction. Add to this the CNS effects which cause depression of respiratory drive. Depression of the cough reflex also occurs. These effects can be particularly problematic for an asthmatic or a patient with COPD or cor pulmonale.

**SLIDE 22:**
Morphine-like compounds at therapeutic doses have relatively modest effects on the CV system. In the supine patient, there are relatively small effects on the bp, cardiac rate and rhythm.

However, there is some peripheral vasodilation and reduced peripheral resistance, as well as an inhibition of the baroreceptor reflex. Therefore, a patient moving from a supine to standing position may experience orthostatic hypotension. Part of the hypotension is due to release of histamine.

There is also some vasomotor depression that plays a role in hypotension.

**SLIDE 23:**
CSF pressure may increase due to increase **pCO2** which causes cerebral vasodilation. If respiration is maintained normally, intracranial pressure will not be increased. Morphine is usually contraindicated in head injury or intracranial lesions, since it will exacerbate the existing increase in CSF pressure. Furthermore, morphine side effects make monitoring of the vomiting, miosis, and CSF pressure increases produced by the medical condition difficult to determine.

**SLIDE 24:**
The GI effects of morphine-like compounds are for the most part inhibitory. In the stomach and small intestine, there is an increase in tone and a decrease in motility. Gastric emptying time is decreased. Passage of small intestine contents is delayed, and more water is absorbed. Propulsive peristaltic waves in the large intestine are suppressed or absent. Further delay in passage of the bowel contents occurs in the large intestine. Anal sphincter tone is increased and defecation reflex is suppressed. These effects lead to constipation.

***Opiates are frequently used for control of diarrhea.***

**SLIDE 25:**
Other effects include the contraction of the bile duct and the sphincter of Oddi.

Renal function may be depressed in part due to ADH release. Urinary retention sometimes occurs because of increased sphincter tone and suppression of the urinary voiding reflex.

Opiates may prolong labor.

**SLIDE 26:**
~~We will discuss tolerance and dependence more in the lecture on drug abuse.~~
I would like to note here that tolerance and physical dependence occurs with repeated use of opiates.
I'd like to point out that a high degree of tolerance occurs to:

Analgesia, Euphoria, Dysphoria, Mental Clouding, Sedation……..

Moderate amount of tolerance occurs to bradycardia.

No tolerance occurs to miosis, constipation, convulsions, and antagonistic actions.

- An addict or a terminally ill individual who is taking opiates chronically typically has miosis and is constipated.

**SLIDE 27:**
What I would like you to know from the first lecture are:
1) Uses of the opioids.
2) You should also know the classes of the opioids, such as agonists, antagonists, mixed agents, and that endogenous ligands exist. Do not memorize anything regarding the endorphins, enkephalins, or dynorphins.
3) Know that there are subtypes of opiate receptors and understand what these receptors do physiologically and pharmacologically.

**SLIDE 28:**

4) Know the characteristics of opiate analgesia- that perception and reaction to pain is altered. Know what kinds of pain opiates are good for.

5) Know the effects of opiates on the GI tract, respiration, cardiovascular function, and cough.

# Narcotic Analgesics II

**SLIDE 29:**

-The opioids are generally well absorbed from the GI tract.
- Some opiates are available as rectal preparations.
-The more lipophilic opiates are absorbed through the nasal or (oral) buccal mucosa.
-Very lipophilic compounds such as fentanyl may be absorbed through the skin.

With respect to oral administration: Some of the opiates have a high first pass effect; the % of the first pass effect varies among patients. Morphine is particularly bad- in fact only about 25% of the oral dose is bioavailable. Contrast this with codeine, in which 60% of an orally administered dose is bioavailable. Morphine can be very effective orally; the dose must be adjusted upward to reflect the high first pass effect.

**SLIDE 30:**

Many of the opioids are given intravenously. The more lipophilic ones enter the brain more quickly than morphine. Only a small % of morphine actually reaches the brain, because of its relatively poor ability to pass the blood brain barrier.
Some opiates have extremely short durations of action, such as fentanyl, which redistributes from the brain to other tissues.

**SLIDE 31:**

The metabolism of morphine-like compounds is through glucuronidation of the 3 or 6 -position OH group. Both heroin and codeine are metabolized, at least in part to morphine. (1)*Indeed as I mentioned earlier it is believed that neither heroin nor codeine nor oxycondone or pharmacologically active themselves, rather they are metabolized to morphine (the active agent).*

Once converted to morphine they, too, are glucuronidated. The glucuronidated morphine is excreted by the kidney. *(2)A second interestingly points is that, morphine-glucuronide is more potent than morphine as an analgesic. Furthermore, in patients taking morphine chronically, it may be responsible for producing most of the analgesic effects of morphine.*

**SLIDE 32:**

**Patient controlled analgesia or PCA** is a relatively new concept that has proven very beneficial to patients who have had major surgery or are being treated chronically with opiates for a terminal illness. An automated device controls the release of the opiate- usually intravenously. The device is programmed with the dose and the dosing interval, which makes the PCA machine very safe. There are many advantages to the PCA machine. One is that the patient can receive the medication on demand. Requesting a dose from nursing staff takes longer, particularly in these days of reduced staffing. The patient can titrate his dose. He may activate his PCA device for a dose and then do it again 20 min later. He may then be locked out for awhile. This regimen provides more uniform pain management. Studies have shown that it actually reduces opiate use overall.

**SLIDE 33:**

One special use of opiates that we have not covered yet, because it did not fit in any other category. That special use is the relief of dyspnea (*dis-p-nea*; difficulty in breathing) caused by pulmonary edema with acute left ventricular failure. The mechanism by which morphine reduces dyspnea is unclear. It may involve a reduction in the patient's fear level and/or the reduction of cardiac workload due to decreased fear and apprehension. The decreased peripheral resistance produced by morphine may also be part of the therapeutic benefit.

**SLIDE 34:**

Let's now consider some individual agents.

First are the strong agonists of the phenanthrene class. We have talked about morphine extensively. Oxycodone is another strong agonist. Heroin, as I mentioned earlier, is 3,6 diacetyl morphine. It is more potent than morphine, crosses the blood brain barrier more readily than morphine. It is metabolized to monoacetylmorphine and morphine in the brain *(the active agents; heroin itself is not pharmacologically active*). Heroin has no accepted clinical use in the US.

**SLIDE 35:**
Methadone is a strong agonist of the phenylheptylamine class. It is qualitatively similar in its analgesic effects as morphine. It also has similar effects on bowel motility, cough, biliary tone, and secretion of pituitary hormones. It has better bioavailability than morphine, so it has a higher oral/parenteral ratio. It also has a longer duration of action than morphine. Methadone is used for its analgesic actions and for heroin addicts.

Tolerance and dependence develop more slowly than that seen with heroin or morphine. Withdrawal from methadone is milder than that with heroin or morphine. Addicts may be placed in a maintenance program where they receive methadone daily. They become dependent and tolerant on methadone and cross- tolerant to the effects of heroin. This cross tolerance prevents some of the addiction-reinforcing effects of heroin. The idea is that the patient is less likely to engage in criminal activity to support his habit and is therefore more amenable to therapy and rehabilitation.

**SLIDE 36:**
Meperidine (meh-pehr-ih-deen) is a strong agonist of the phenylpiperidine class. Meperidine is less potent than morphine but has better bioavailability when given orally. In contrast with morphine it has less action on the bowel and is not particularly constipating. It has no antitussive action. Its antimuscarinic effects can be problematic for some patients. For instance, it can produce tachycardia. It is reported to have a negative inotropic effect. Its metabolite, normeperidine has been linked to production of seizures. These problems limit its use in a number of patients. Meperidine does not hinder labor and produces less respiratory depression in the newborn. Therefore, it is more commonly used in labor and delivery than morphine.

**SLIDE 37:**
Other members of the phenylpiperidine class are fentanyl (fen-tuh-nil) and sufentanyl (sue-fen-tuh-nil). These are structurally related to meperidine. They are more potent than morphine and sufentanyl is more potent than fentanyl. They are short acting and are very useful in surgery as a part of balanced anesthesia. They are frequently used postoperatively. [*Just as an aside in the response to the Moscow theater hostage standoff in 2002; the Russian are believed to have used fentanyl gas to incapacitate the terrorists/hostages]*.

**SLIDE 38:**
Codeine is a member of the phenathrene class because of it's a congener of morphine. Codeine is a moderate agonist; it is much less potent than morphine. In fact its analgesic activity is probably due to 10% of an administered dose that is metabolized to morphine. It is commonly combined with ASA or acetaminophen for analgesia. Many of you have probably taken Tylenol #3, which has 30 mg of codeine.
-Codeine has a direct action on the receptors in the cough center and is an excellent antitussive. As an antitussive, codeine is usually present in a hydroalcoholic solution.

**SLIDE 39:**
Propoxyphene (pro-pox-ee-feen) is another member of the phenylheptylamine class and is structurally related to methadone.

*It is not that potent and **in the past** was frequently given with aspirin (Darvon) or acetaminophen (Darvocet). It is not an effective cough suppressant.* July 9, 2009: While FDA advisory panel votes to ban propoxyphene containing drugs from Market- FDA instead requires change in labeling to strongly warn of overdose potential.

Other alternatives: *Percocet (oxycodone + acetaminophen) Percodan (oxycodone + aspirin)*

**SLIDE 40:**
Diphenoxylate (die-fen-ox-ih-late) and Loperamide (low-pehr-uh-mide) are mild agonists of the phenylpiperidine class. Diphenoxylate is not analgesic at standard dosages and its insolubility makes it of very low abuse potential for parenteral administration. Loperamide does not cross the blood brain barrier to a significant degree. These 2 agents are used for their antidiarrheal action.

**SLIDE 41:**
The mixed agonists/antagonists were developed to provide analgesia equivalent to morphine but with less addictive liability. Generally, these compounds are kappa agonists and either marginally agonistic at mu receptors or inhibitory at mu receptors.
*With the opiate epidemic- these use of these agents has increased dramatically in recent years.*

**SLIDE 42:**

Pentazocine (pen-taz-oh-seen) is a benzomorhan that has **weak partial agonist or antagonist action at the mu receptor. It is a good agonist at the kappa receptor**. Pentazocine is used frequently as an analgesic, but it is less potent than morphine. It is particularly useful in individuals who have chronic severe pain or those who have drug abuse problems.

-While it does have abuse liability, it is less likely to be abused than morphine. Orally administered pentazocine has less addictive liability than parenterally administered pentazocine.

-Because of its mixed action at mu receptors, pentazocine will ppt withdrawal in an individual addicted to strong mu agonist opioids.

-Pentazocine produces similar respiratory depression as morphine at equianalgesic doses, but produces less respiratory depression at high doses.

-Repeated high doses can produce hallucinations and high blood pressure. It can increase cardiac workload.

**SLIDE 43:**

Butorphanol (byoo-tore-fan-ahl) is a **mu receptor antagonist/partial agonist and kappa agonist**. Its abuse potential is extremely low, so it is not a scheduled drug. It is more potent than morphine. Two to three mg of butorphanol produces the analgesia that 10 mg of morphine produces. It can increase cardiac workload, so it isn't useful for MI. Major side effects are nausea, sweating, drowsiness, and feelings of floating.

**SLIDE 44:**

Buprenorphine (byoo-pre-nore-feen) is a semisynthetic opioid derived from thebaine, one of the compounds found in the poppy plant. Its analgesic and other CNS effects are similar to morphine. **It is a partial agonist at the mu receptor, but may be a kappa antagonist**. It is more potent than morphine. 0.4 mg of buprenorphine is comparable to 10 mg of morphine.

-This drug illustrates two diverging pharmacological principles: that of potency and efficacy. Potency is reflected in the lower dose that is needed relative to that of the morphine dose. However, since it is only a partial agonist, buprenorphine does not have the same efficacy as larger doses of morphine. That is why buprenorphine can ppt withdrawal in addicts if their opiate of choice is immediately replaced with buprenorphine. Since it has significant activity at mu receptors, it has addictive liability. It is therefore a scheduled drug.

◆The partial agonist, buprenorphine, is commonly prescribed to treat opioid dependence or addiction, but it may also be used off-label as an analgesic. Unlike pure opioid agonists, it has a dose-ceiling effect, where the analgesic and subjective effects, such as euphoria, reach a plateau, thereby limiting abuse potential.

**SLIDE 45:**

Opioid antagonists have little physiological effects on a person who is not taking opioids.

These antagonists are primarily given to individuals to reduce the effects of mu or kappa agonists.

- They are particularly useful in cases of narcotic poisoning. The diagnosis of an addiction to opioids can be accomplished with opioid antagonists, but care must taken not to ppt a full blown withdrawal.

- Small doses of antagonists may also be used to reduce the SE of epidural or intrathecal opiates without affecting the analgesia.

- Reduction of respiratory depression in a neonate whose mother has received opioids is also a use.

-Treatment of compulsive opioid abuse has been tried. Once the opiate addict has been withdrawn and is drug-free, then theoretically blockade of opiate receptors will cause a failure of subsequent drug administration to produce reinforcing euphoric effects.

- Alcoholism has been treated with some degree of success with oral naltrexone. Antagonists do not block the effects of alcohol, such as intoxication, nor do they block the effects of alcohol poisoning. They do seem to reduce craving. In a certain % of alcoholics, reduced drinking

and/or a lower rate of relapse has been demonstrated. Counseling or group therapy appears to be critical for the success of naltrexone.

**SLIDE 46:**

**Naloxone** is a rapid acting antagonist of very short duration that is very useful in opiate poisoning. The duration of action is short, regardless of the route, so the patient may need additional doses. If an addict is being treated for overdose, it is possible to titrate the dose of naloxone so that respiratory depression is reduced, but withdrawal is not ppted. Naloxone will not reverse the respiratory depression produced by other sedative hypnotics. If a person has coadministered large amounts of barbiturates or has alcohol poisoning, naloxone will not reverse the resulting respiratory depression.

**SLIDE 47:**

**Naltrexone** is a more orally effective antagonist due to its long half-life. It is marketed as ReVia for treatment of alcoholism. It can cause hepatic problems, so liver function must be monitored.

**SLIDE 48:**

**Naloxegol (Movantik)** This is a PEGylated form of Naloxone which does not penetrate the blood brain barrier (more precisely PEGylation increases efflux by P-glycoprotein) and therefore it only antagonizes mu receptors that are located peripherally. It is used to treat opioid-induced constipation in adults with chronic non-cancer pain (FDA approved September 2014).

**SLIDE 49:**

Acute opiate toxicity may result from several scenarios: clinical overdose, accidental overdose in an addict, or attempted suicide. The patient mental status may range from stuporous to profound coma. Respiratory rate will be low- 2 to 4 breaths per min. As respiratory exchanges decrease, bp will fall. Pupils will be pinpoint and symmetrical, unless hypoxia is very severe. In that case, pupils may be dilated. ***The triad of coma, pinpoint pupils, and depressed respiration*** are strong indicators of opiate poisoning. Body temp falls, convulsions may occur, and skeletal muscles are flaccid. Death is almost always from respiratory failure.

**SLIDE 50:**
Treatment centers on maintaining the patient's airway and reversing the effects of the opiates with opiate antagonists. However, addicts are very sensitive to antagonists. A dose that reduces the respiratory depression, but that does not ppt withdrawal should be given. It is important to bear in mind that addicts and suicide attempters may use multiple drugs. Opiate antagonists do not block to any significant degree the sedative effects of sedative/hypnotics.

**SLIDE 51:**
Dextromethorphan is the d isomer of levorphanol, an analog of codeine. Dextromentorphan does not work at opiate receptors. It works directly on cough centers in the brain. It is present in many over the counter cough preparations, such as Robitussin DM.

◆ Abuse Potential: At high doses (10-50 x) DM acts as a hallucinogen/dissociative anesthetic, acting as a NMDAR antagonist.

**SLIDE 52:**
For the drugs in the drug list:

1) Know whether they are agonists, mixed agonists/antagonists or partial agonists (drugs that are in lecture script and ppt).
2) Know uses and limitations. For instance, codeine has less efficacy than morphine. It's still useful as an analgesic, but it is also extremely good as an antitussive. Meperidine is a good analgesic, but is very poor as an antitussive or antidiarrheal agent. Diphenoxylate and loperamide are good antidiarrheal drugs, but are ineffective as analgesics. I never ask anything about structures or chemical classes of drugs.

**SLIDE 53:**

3) Be familiar with the use of opiate antagonists for treatment of opiate poisoning.

First Aid Basic Sciences Organ Systems, 2nd Edition: Chapters 5 and 6.