GENERAL ANESTHETICS

History of early anesthetics: Early drugs essentially provided “controlled suffocation” of the patient
● No longer used: Ether (explosion danger); chloroform (carcinogen, explosion danger)
● Still used: Nitrous oxide – see below

FOUR DESIRED COMPONENTS OF GENERAL ANESTHESIA

1. Unconsciousness
2. Amnesia – Patient doesn’t remember what happened just before, during, or right after surgery
3. Analgesia – Lack of pain and autonomic stability (generally go hand-in-hand)
   a. Intact autonomic responses can indicate pain or discomfort via changes in heart rate, BP, etc.
4. Muscle relaxation – Especially important for orthopedic and abdominal surgery

INHALATION ANESTHETICS – GENERAL PRINCIPLES

<table>
<thead>
<tr>
<th>MAC (Minimum alveolar concentration)</th>
<th>The concentration of anesthetic that prevents response to a standard painful stimulus in 50% of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expressed as % of inhaled anesthetic gas or vapor mixed in O2</td>
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<tr>
<td></td>
<td>1/MAC = potency (smaller MAC = more potent anesthetic)</td>
</tr>
</tbody>
</table>

Dose altering factors (MAC-altering factors) | Many factors, including but not limited to body temperature, pregnancy, age, concomitant use of other anesthetics or adjuncts

Blood/Lipid solubility & pharmacokinetics

Blood solubility: ↑ blood solubility → slower induction (onset of anesthesia)
Lipid solubility: ↑ lipid solubility → faster induction (and longer duration)

- Imagine the blood as a sponge for the inhaled anesthetic; the anesthetic travels from the lungs, saturates the blood, and finally gets to the brain to induce anesthesia
- High blood solubility is kind of like a super-absorbent sponge. Anesthetic will take a long time to saturate the “blood compartment” and “spill out” into the brain.
- With low blood solubility, lesser amounts of local anesthetic are needed to saturate the “blood compartment” before the anesthetic can “spill out” into the brain.

Mechanism(s) of action are unclear

- Most probable explanation – Selective effects on specific neurons, and more specifically some “potentiation” of GABA’s neuronal inhibitory effects
- Other potential explanations: ↑ membrane fluidity, membrane hyperpolarization

“Stages & Planes” of general anesthesia

Outmoded “indicator” of adequacy or degree of general anesthesia (don’t memorize!!)
- Analgesia (w/o amnesia)
- Excitement – Initially, inhibitory neuronal pathways are selectively put to sleep
- Surgical anesthesia – Entire CNS depressed
- Medullary depression, coma, death

IV INDUCTION DRUGS – GENERAL PRINCIPLES

● Good to excellent amnesia and unconsciousness (some give anterograde & retrograde amnesia)
● Virtually no analgesic or muscle relaxant activities
  ○ Adjuncts for surgical anesthesia
MALIGNANT HYPERTHERMIA, HALOTHANE, AND SUCCINYLCHOLINE

- Results from interaction of any volatile liquid anesthetic and any neuromuscular blocker
  - Interaction of halothane and succinylcholine is most common
- Incidence & outcome: 1/50000 adult cases and 1/15000 peds cases; fatal 80% worldwide, 10-20% in U.S.
- Genetic predisposition: Family history and screening important
- Timeframe: Can occur intra-operatively or post-operatively several hours after drug exposure
- Pathophysiology: ↓ sarcoplasmic reticulum Ca uptake → titanic muscle contraction → profound, rapidly developing fever → K+ may leak out due to sarcolemma damage
  - Leads to ventilatory impairment, hyperkalemia, arrhythmias, fever-induced seizures
- Management: Dantrolene sodium, oxygen, ↓ body temperature, supportive care and other drugs as needed

IV INDUCTION-MAINTENANCE DRUGS ARE SHORT-ACTING NARCOTICS → FENTANYL (PROTOTYPE)

- Similar to morphine but more potent
- Neuroleptic analgesia: Fentanyl combined with Droperidol (Tranquilizer)
- Can be given transdermally for chronic pain management
- High IV doses used as primary anesthetic for special procedures (e.g. cardiac surgery)

<table>
<thead>
<tr>
<th>Class / prototype</th>
<th>Pharmacokinetics &amp; use</th>
<th>Effects</th>
<th>Interactions and negative effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHALED VOLATILE LIQUID AGENTS</strong></td>
<td><strong>MAC &lt; 1% inspired air</strong></td>
<td>- VERY potent</td>
<td></td>
</tr>
<tr>
<td>- Halothane</td>
<td><strong>Administration:</strong> Usually 0.5-1% Halothane + 60-70% NO + balance O2</td>
<td><strong>Dose-dependent organ system effects</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Excretion:</strong> 70-80% unchanged by lungs</td>
<td><strong>CNS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Use:</strong> Maintenance of surgical anesthesia</td>
<td>- Excellent amnesia, unconsciousness, analgesia</td>
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<tr>
<td></td>
<td></td>
<td>- Cerebral vasodilation → ↑ ICP (bad w/ stroke &amp; cancer pts)</td>
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<td><strong>CV-RENAL</strong></td>
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<td>- ↓ HR, ↓ SV, ↓ CO, ↓ BP, ↓ urine output</td>
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<td></td>
<td></td>
<td>- Potential (intrinsic) arrhythmogenicity; catecholamines can exaggerate this effect</td>
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<td></td>
<td></td>
<td><strong>Pulmonary:</strong> Bronchodilator; reverses/prevents bronchospasm</td>
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<td></td>
<td></td>
<td><strong>SKELETAL MUSCLE</strong></td>
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<td></td>
<td></td>
<td>- Relaxation insufficient for surgery</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Malignant hyperthermia risk w/ succ. (See p. 1)</td>
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<td></td>
<td></td>
<td><strong>Uterine:</strong> Relaxant</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Hepatic:</strong> “Rare” fulminant hepatotoxicity +/- necrosis</td>
<td></td>
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<tr>
<td>Others include Isoflurane (most widely used in US), Enflurane, and Sevoflurane.</td>
<td></td>
<td></td>
<td><strong>↑ Risk of catecholamine-induced arrhythmias</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↑ Cardiac depression when used w/ b-blockers or Ca-channel blockers</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- ↑ Respiratory depression w/ narcotics</td>
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<tr>
<td></td>
<td></td>
<td>- Need for intubation, ventilator</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↑ Action of nondepolarizing (curare-like) NMJ blockers; prolonged muscle paralysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Malignant hyperthermia risk w/ succinylcholine (see p. 1)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td><strong>Acute OD/toxicity: CV depression</strong></td>
<td></td>
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</tbody>
</table>
INHALED GASES
- Nitrous oxide

MAC = 105% inspired air
- Not potent enough to get analgesia in 50% of pts, even at 100% NO w/ no O2!!

Administration:
See above
See rapid onset and recovery

Gives modest analgesia, amnesia, unconsciousness, but no muscle relaxation

Organ system effects
- Modest cardiovascular depression
- Little/no uterine effects

Long-term/repeat exposure
→ Neurologic Sx that look like vitamin B12 deficiency

Additional concerns about mutagenicity, carcinogenicity, and teratogenicity
- Why OR ventilation is so good

IV INDUCTION DRUGS

BARBITURATES
- Ultra-short acting
- Good to excellent amnesia and unconsciousness w/ virtually no analgesic or muscle relaxant activities

Thiopental, Thiamylal, Methohexital

↓ Cerebral blood flow, metabolic rate, ICP (desirable)
- Induction risks
  - CV depression
  - Laryngospasm + resp. depression / apnea

BENZODIAZEPINES
Midazolem
- Used for induction and “conscious sedation”
- Good sedation, excellent amnesia

Midazolem, Diazepam, Lorazepam – limited use
- Slow onset and long actions

KETAMINE
- “Dissociative” anesthetic w/ excellent amnesia, analgesia, unconsciousness
- Good for high risk pts (hypovolemic, hypotensive), children (eases induction), asthmatics (bronchodilator), burn pts (grafts, debridement)

Autonomic reflexes intact; often activates sympathetics
Potential psychomimetic actions (PCP relative)

ETOMIDATE
Good for short procedures or pts at risk for benzodiazepines
- Rapid onset, brief duration
- Excellent amnesia, unconsciousness
- No analgesia, muscle relaxation

Negligible CV or respiratory effects
Potential myoclonus on injection

PROPOFOL
- Chemically unrelated to others
- Rapid onset (<1 min), short duration (<10-15 min)
- Excellent amnesia, unconsciousness
- Little/no analgesia, muscle relaxation
- Popular for ambulatory surgery

Blunts autonomic-CV responses to intubation

PHARMACOLOGY OF ANALGESICS

Narcotic Analgesics
• Morphine (prototype)
• Levophanol
• Meperidine
• Methadone
• Etorphine

Competitive agonists
• Naloxone
• Naltrexone

Mixed agonists-antagonists
• Nalorphine
• Pentazocine
• Nalbuphine
• Butorphanol
• Buprenorphine
**Codeine**  
**Propoxyphene**  
**Fentanyl**  

**RELATED SPECIFIC AGENTS**  
- Apomorphine  
- Dextromethorphan  
- Diphenoxylate  
- Loperamide  

A.k.a partial agonists  
- Can activate same receptors as full agonists with smaller effects  
- Antagonize the actions of the agonists (so that agonists give lesser effect)  
- Therapeutically, the least interesting

**** Drugs to know…they are italicized on this table…not in the table → *Alfentanil* and *tramadol*

Narcotics act via receptor-mediated actions  
- Opioid receptor types: m (named for morphine; tolerance inducing); k  
- Tolerance, dependence, cross-tolerance, and cross-dependence – More on this later

### Characteristic morphine-like effects of narcotic analgesics

<table>
<thead>
<tr>
<th>Analgesia</th>
<th>STRONGEST ANALGESICS KNOWN</th>
</tr>
</thead>
</table>
|           | Effective when pain comes from injury or inflammation; mechanism poorly understood  
|           | ▪ Not effective for deafferentation pain  
|           | Two components of morphine analgesia  
|           | ▪ **Reduction in pain sensation:** Quantitatively reduces pain neurotransmission  
|           | - Pre-emptive pain relief: Certain pain receptors uncovered only w/ inflammation; dripping morphine into surgical wound sites can prevent these receptors from getting activated  
|           | ▪ Reduction in the subjective distress produced by the pain sensation  

| Subjective effects | - Distinctive  
|                   | - **Situationally dependent:** Addicts get a “good sick,” those w/ pain have less pain, those w/o pain primarily experience side effects  

| Overall sedation | Occurs at all doses where pain relief occurs: Includes ↓ most behaviors, ↓ muscle tone, ↑ dozing, waxing/waning awareness, mental clouding, staring into space; sedation → severe depression → coma w/ ↑ dose  
|                  | ▪ Effect on sleep: Unnatural form of sleep w/ no REM activity  
|                  | ▪ Species difs in char of effect: Primates & humans similar; cats & rodents get stimulant effects  

| Respiratory depression | **Strong respiratory depressants** → Dose-dependent reduction in medullary sensation of CO2  
|                        | ▪ Occurs at standard clinical analgesic doses  
|                        | ▪ **Small margin of safety:** Slight OD can lead to severe respiratory depression, including apnea  
|                        | ▪ w/ morphine, 4x the analgesic dose is lethal for most people  
|                        | ▪ Potentiation factors: Debilitating conditions, administration of barbiturates or phenothiazines  

| Other CNS effects | - N/V: Common  
|                  | - Vertigo (ambulatory pts)  
|                  | - Miosis  
|                  | - Release of ADH (get tolerance)  
|                  | - Cough suppression  
|                  | - Truncal rigidity (prob in OR)  
|                  | - Convulsions w/ overdose or abuse (e.g meperidine, propoxyphene)  


### Morphine-like effects of narcotic analgesics under ANS control

| GI tract | Constipation: Occurs at ↓ doses than used for pain relief; dose-related effect; no dev. of tolerance |
| Smooth muscle | ↑ tone of biliary tract muscle: ↑ pressure in bile ducts; sometimes get biliary colic  
| | - Also see ↑ tone in bronchial smooth muscle, ureters, and urinary bladder |
| Cardiovascular | Dose-dependent; not usually a major problem  
| | - Large doses given IV → Hypotension via ↓ peripheral vascular resistance  
| | - Standard clinical doses → May produce orthostatic hypotension |
| Neurohumors and transmitters | Rat facts → Don’t help us understand how narcotics act in CNS  
| | - Inhibit ACTH release, Ach release from certain post-ganglionic parasymp fibers (similar effect in rodent CNS), and NE release from some post-ganglionic symp fibers  
| | - Release of adrenal epinephrine, histamine (asthma probs)  
| | - Increased synthesis and turnover of NE in rodent CNS |

### Pharmacokinetics of narcotic analgesics using morphine as prototype

| Mechanism of action | Identification of receptors in CNS  
| | - Techniques: Use radiolabeled morphine stereoisomers; active form binds receptors  
| | - Distribution: All over, but esp. in the head (in general) and the base of the brain (specific)  
| | Receptor effector mechanisms (opioid receptors): G protein-linked, inhibition adenylyl cyclase, activation of K+ channels, suppression of voltage-gated Ca++ channels  
| | - Leads to blockade of NT release (e.g. glutamate, substance P) → Block pain transmission  
| | Endogenous opiates: Identification of morphine-like substances  
| | - Pro-opiomelanocortin: Active form b-endorphin; mimics morphine better than any other endogenous opiate  
| | - Proenkephalin: Met-Enk or Leu-Enk domain  
| | - Prodynorphin: Dynorphin has slight preference for k receptor; may be k endogenous ligand  
| | - Physical and pharmacological properties: Brief & small biological activity; only pathological activity/injury results in measurable (but small) levels of these compounds  
| | - Modulation of pain experience not well-understood: Concept of “runner’s high” pharmacologically shaky |

| Absorption, distribution, and fate | Absorption: Poor from GI tract; relatively well subcutaneously or IM  
| | Distribution: Onset of action (by subcutaneous route) related to lipid solubility  
| | - Controls access to central receptors; ↑ solubility → ↑ absorption  
| | ELIMINATION/DETOXIFICATION  
| | - Major path: Conjugation w/ glucuronic acid to morphine 6-glucuronide (more active than morphine) or morphine-3-glucuronide (inactive)  
| | - Minor path: N-demethylation to inactive form  
| | Duration of action: 4-6 hours |

### Pharmacologic principles of morphine-like narcotic analgesics

- Produce morphine-like CNS depression in single doses  
- Induce similar subjective effects & reinforce self-administration behavior  
- CNS depressant effects antagonized by naloxone (via competitive inhibition at receptor site)  
- Upon repeated administration, tolerance develops to CNS depressant effects
- Cross-tolerance among drugs, regardless of chemical structure
- Tolerance at level of receptor activation (not drug structure)
- Upon repeated administration, *drugs produce physical dependence of the morphine type*
- *Cross-dependence among narcotic analgesics*
  - An organism physically dependent on any one narcotic analgesic will have its dependence supported by another drug of this class.
  - Abstinence syndrome produced by drug withdrawal can be relieved by any compound of this class (similar to cross-tolerance)
  - W/physical dependence on any narcotic analgesic, *administration of narcotic antagonist will precipitate an abstinence (withdrawal) syndrome*, regardless of chemical structure of the drug

### Characteristics of morphine-type tolerance
- **Origin of tolerance**
  - Metabolic: Narcotics metabolized more rapidly through induced p450 system
  - Cellular: Involves receptor recycling through cell (can see dependence w/o tolerance)
  - Learned: Patients w/ pain become tolerant more rapidly than those w/o pain
- **Magnitude of tolerance**: Depends upon specific biological effect
  - Little tolerance to constipation; considerable tolerance to analgesia
- **Augmented by ↑ frequency, ↑ dose of narcotic analgesics**

### Characteristics of morphine-type dependence
- *Morphine abstinence syndrome (withdrawal syndrome)*: Wide set of changes produced upon termination of repeated morphine administration
  - Begins ~ 6 hrs after last dose: Sensation of illness similar to common cold
  - Restlessness, ↑ distress, anorexia, rhinorrhea, lacrimation, perspiration, abdom cramping
  - Restless sleep, possible followed by insomnia
  - Dilated pupils, N/V, diarrhea, spasms of flexor muscles of the legs
  - Elevated body temperature, heart rate, systolic & diastolic blood pressure
  - **Peak severity**: 36-48 hrs following last dose; recovery requires ~ 2 wks
- **Dependence w/ shorter[longer]-acting narcotics**: Peak withdrawal severity sooner [delayed]

### Other Morphine-like agonists
- **Levorphanol**
  - Morphinan: Similar chemical structure to morphine
  - *Full spectrum of morphine-like effects w/ better oral-parenteral potency ratio*
  - **Dextromethorphan**: Prototype non-narcotic antitussive
  - Dextro isomer of the codeine analogue of levorphanol
  - Suppresses cough by central mechanisms not well understood (and not that great, either)
  - In therapeutic doses, produces little sedation or GI disturbance
  - High doses produce respiratory depression
  - Actions are unaffected by narcotic antagonists; shows no cross-tolerance to morphine
  - Low risk with regard to abuse liability

- **Meperidine**
  - *Shorter duration of action than morphine*: Frequently used by dentists
  - Phenylpiperidines w/ *full spectrum of morphine effects*
  - Concurrent MAO inhibition produces a severe state of CNS excitation w/ delirium, hyperpyrexia, and convulsions, *or respiratory depression w/*
**hypotension**
- N-demethylation produces a metabolite that has stronger excitant property

**Dephenoxylate and Loperamide (Imodium):** Meperidine congeners
- Constipating agents used as antidiarrheal agents
- Diphenoxylate tablets contain an inactive amount of atropine
- Highly insoluble salts: Activate opiate receptors in GI tract but not centrally
- Antagonizable by narcotic antagonists

### Methadone
- Structure / actions: Has pseudopiperidine ring; a m agonist full morphine-like actions
- Well absorbed orally w/ slightly less sedative effect claimed by advocates
- Use in treatment of heroin abuse
- Given orally 1/day to sustain morphine dependence w/o withdrawal induction
- Considered an effective public health measure, but it’s a long-term treatment w/ frequent relapses as methadone doses reduced
- a-acetylmethadol: Recently approved agent for use in treatment of heroin abuse
- Similar to methadone but longer-acting; patients could come to clinic less often

### Etorphine
- Structure / actions: Oripavine structure; highly potent, short-acting drug
- Used as an immobilizing agent (veterinary practice)
- Marketed as a package w/ its “own” antagonist, diprenorphine

### Fentanyl
- Structurally related to phenylpiperidines (e.g. meperidine)
- Produces strong analgesia, similar to morphine
- Combined w/ a butyrophenone (Droperidol): Produces neurolept analgesia, and can be used for major surgery w/o any other kinds of drugs
- Patches and lollipops available for chronic pain and children’s surgeries, respectively
- Related compounds
  - Sufentanil
  - Alfentanil: Ultra-short-acting compound, w/ action rapidly terminated by metabolism
  - Remifentanil: Most widely used short-acting m agonist; rapid metabolism means administration requires an infusion pump

### Apomorphine
- Similar chemical structure to morphine
- Stimulates CTZ to induce N/V w/ little other narcotic-like effects
- Investigational use as a dopamine-receptor stimulant
- Use in treatment as an emetic
- Emetic effect antagonized by narcotic antagonists (according to some “authorities”)

### “Weak” agonists
Use in milder forms of pain
- Codeine
  - Structure: Morphine w/ methyl in 3 position; weak affinity for m receptor
  - High oral: parenteral potency ratio
  - Low doses relieve cramps, earaches (in children) w/ relatively small risk of abuse
  - Striking CV effects occur w/ non-oral administration
- Porpoxyphene (Darvon)
  - Structure: Similar to methadone
  - Side effects: Similar to narcotics
  - High doses: Excitant effects culminate in convulsions w/ respiratory depression
  - Slight risk of abuse, esp. considering wide use in medicine and dentistry

**Characteristics of pure narcotic antagonists (naloxone, naltrexone, nalmefene are prototypes)**
- Surmountable antagonists of the specific effects of narcotics (reduces potency of agonist)
  - Little effect when given alone, showing that endogenous opiates are not very active under normal circumstances
In narcotic-dependent patient, narcotic antagonist administration elicits a syndrome resembling narcotic withdrawal.

- Syndrome obtainable w/ very small doses of antagonists.
- Duration of action differentiates the three antagonists.
  - Naloxone: Short duration of action; multiple doses may be required to control agonist overdose; should only be used to diagnose narcotic intoxication.
  - Naltrexone: Longer-acting; approved for treatment of alcoholism (unclear mechanism)
  - Nalmefene: Slightly longer-acting than naltrexone
- When administered to normal, drug-free individuals, they are w/o effect except at very high doses.
- Use in diagnosis and treatment of overdose; suggested as diagnostic aid in methadone programs.
- All three antagonists more active in reducing m receptor effects than k receptor effects.

Char. of Morphine-like agonist/antagonists (Nalbuphine, butorphanol, dezocine, buprenorphine, tramadol)

<table>
<thead>
<tr>
<th>Variable effects</th>
<th>- Partial agonist activity at m receptor</th>
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<tbody>
<tr>
<td></td>
<td>- Can have other effects at other receptors</td>
</tr>
<tr>
<td></td>
<td>- e.g. buprenorphine is competitive antagonist at k receptor</td>
</tr>
<tr>
<td>Agonist actions</td>
<td>- Respiratory depression is limited</td>
</tr>
<tr>
<td></td>
<td>- Analgesia is adequate, but may be limited as well</td>
</tr>
<tr>
<td></td>
<td>- Pattern of adverse reaction is similar to Morphine</td>
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<tr>
<td></td>
<td>- Subjective effects similar to Morphine, although limited (actions present in reduced form)</td>
</tr>
<tr>
<td></td>
<td>- Reinforce self-administration behavior</td>
</tr>
<tr>
<td>Antagonist actions</td>
<td>- Precipitate withdrawal in Morphine-dependent patients</td>
</tr>
<tr>
<td></td>
<td>- High dose effects of Morphine-like agonists are antagonized</td>
</tr>
<tr>
<td>Cardiovascular actions</td>
<td>Different: Not yet clear whether the differences are related to opioid receptor actions</td>
</tr>
<tr>
<td>Drug classification</td>
<td>Currently marketed compounds not classified under the Controlled Substances Act</td>
</tr>
<tr>
<td></td>
<td>- Exception: Buprenorphine</td>
</tr>
</tbody>
</table>

Kappa-receptor mediated agonist actions

- Analgesia
- Diuresis/water type
- Tolerance, dependence, but no cross-tolerance or cross-dependence w/ morphine
- Subjective effects that are “dysphoric”
- Fail to reinforce drug-taking behavior
- Absence of significant respiratory depression (kill animals by induced convulsions; unclear if these convulsions are receptor-mediated)
- All actions reversed by narcotic antagonists (w/ possible exception of convulsant action)

Char. of narcotic antagonists w/ Morphine-like agonist effects (nalorphine, cyclazocine, levalorphan)

- Some mixed agonists/antagonists have action at k receptor (pentazocine)
- Some produce nalorphine-like actions mediated at a k receptor – CNS depression, analgesia, sedation, depression of respiration, and ataxia, along w/ dysphoria and hallucination
- Pharmacologic prototypes; not marketed
- Do not reinforce self-administration behavior
- CNS depressant effects cannot be antagonized by nalorphine, but can be blocked by large doses of naloxone (surmountable antagonist)
- Cross-tolerance develops for compounds that work at the k receptor, but not for those w/ morphine-like actions, suggesting that the receptors do not have any significant cross-talk w/ each other
- Physical dependence develops but not cross-dependence w/ m-like compounds.