Pain

- Brings patients to the DRs

- Fear can keep the patient from going to the Drs at appropriate time

- Treatments are often done on the inflamed, hypersensitive tissues of a patient

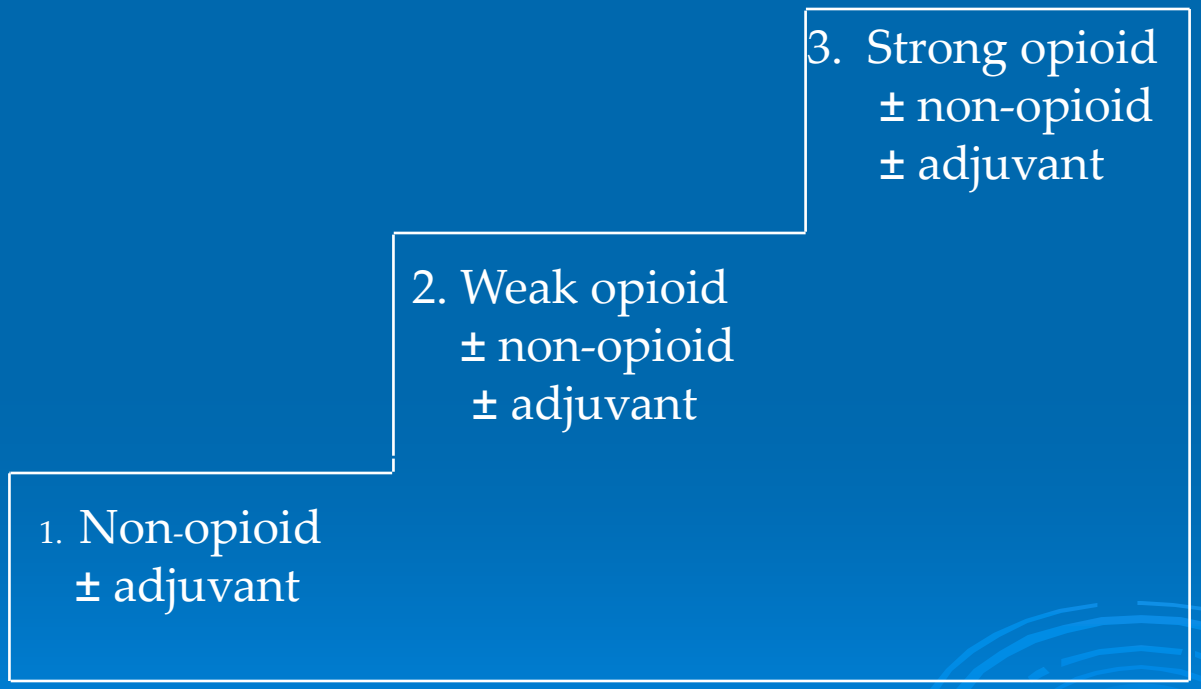
- Pain is a symptom of a pathologic condition that needs to be taken care of:

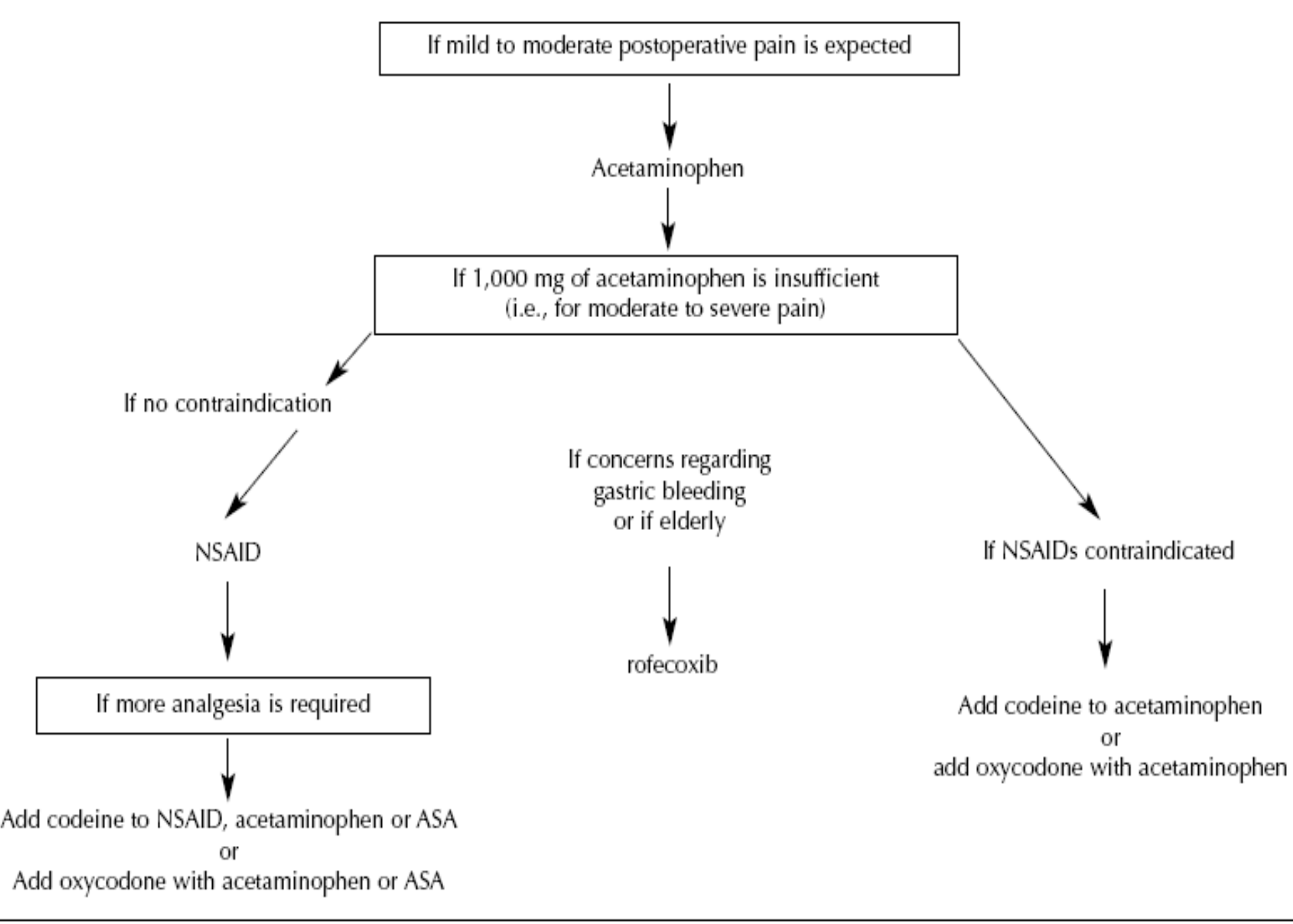
– no treatment, still pain.

– Induced by the release of histamine, serotonin, prostaglandins, bradykinins,etc. that activate pain signaling.

WHO analgesic ladder

Pain persists or increases → Pain persists or increases → Pain




If mild to moderate postoperative pain is expected
Acetaminophen
If 1,000 mg of acetaminophen is insufficient
(i.e., for moderate to severe pain)
If no contraindication
NSAID
If more analgesia is required
Add codeine to NSAID, acetaminophen or ASA
or
Add oxycodone with acetaminophen or ASA
If concerns regarding
gastric bleeding
or if elderly
rofecoxib
If NSAIDs contraindicated
Add codeine to acetaminophen
or
add oxycodone with acetaminophen

Opioid analgesics

- **All drugs in this category act by binding to specific Opioid receptors in CNS to produce effects that mimic the action of naturally occurring substances, called *endogenous opioid peptides* or *endorphins.***

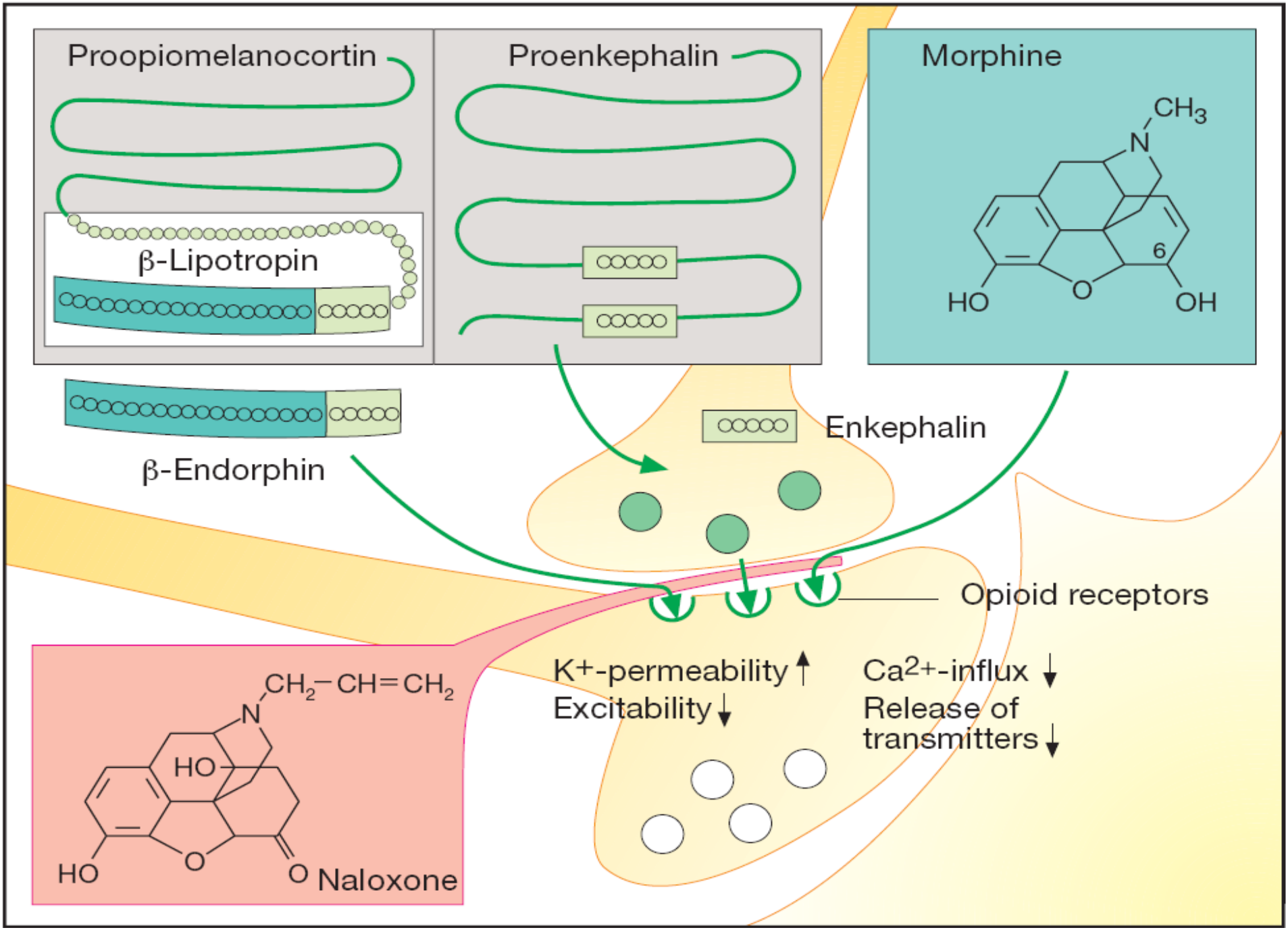
- **Exert their major effect by interacting with Opioid receptor in the CNS, and in other places such as GI tract and urinary bladder.**

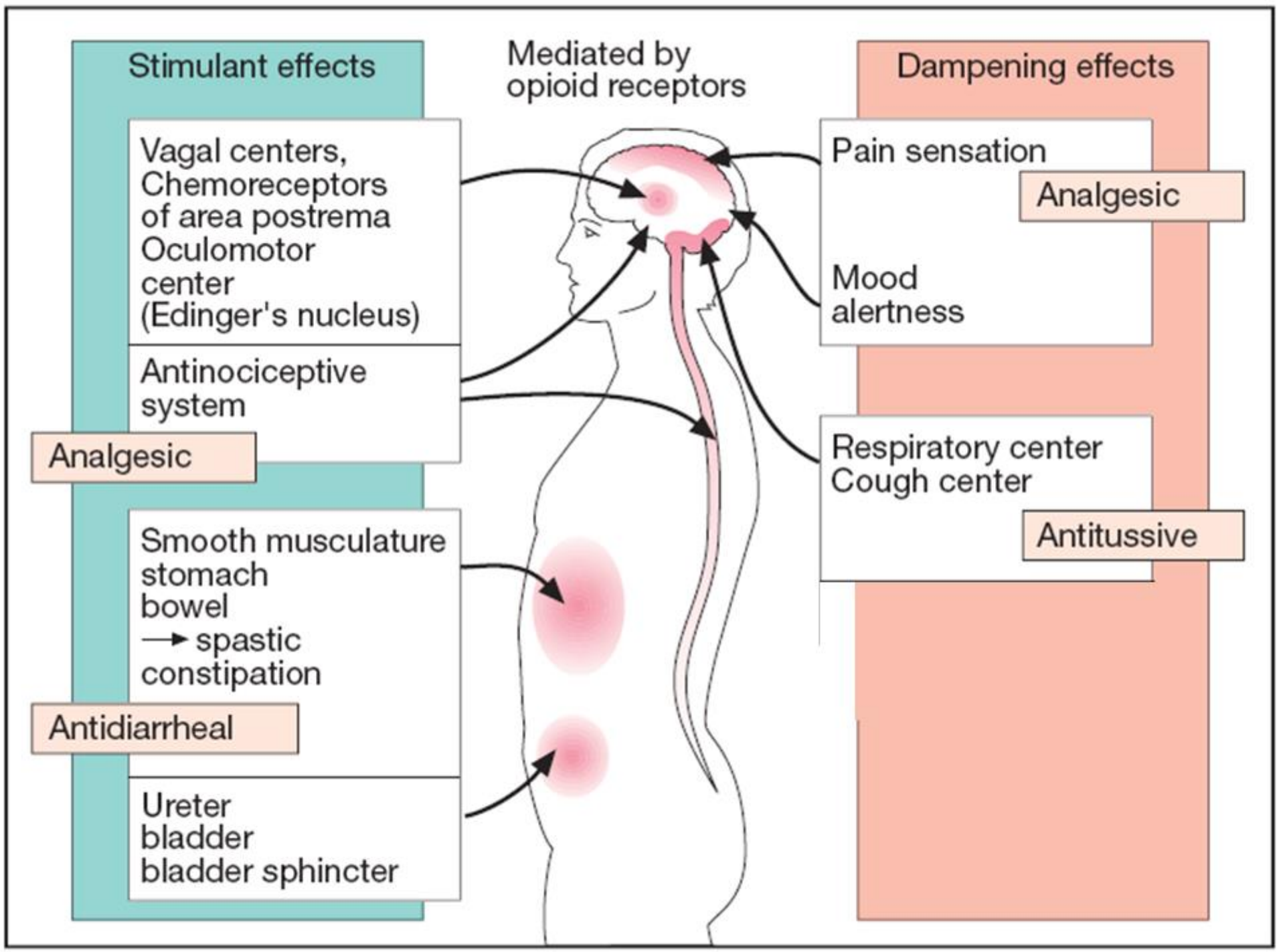
- **Opioids cause hyperpolarization of nerve cells, inhibiting nerve firing, and presynaptic inhibition of transmitter release.**

- **Morphine causes analgesia, and patients treated with morphine are still aware of the presence of pain, but sensation is not unpleasant.**

Opioid Analgesics: Indications

- Main use: to alleviate moderate to severe pain
- Cough centre suppression
- Treatment of diarrhea
- Balanced anaesthesia


Proopiomelanocortin
β-Lipotropin
Proenkephalin
Morphine
CH3
N
6
HO
O
OH
β-Endorphin
Enkephalin
Opioid receptors
K+-permeability
Excitability
Ca2+-influx
Release of transmitters
CH2–CH=CH2
N
HO
HO
O
O
Naloxone


Stimulant effects
Mediated by opioid receptors
Dampening effects
Vagal centers, Chemoreceptors of area postrema Oculomotor center (Edinger's nucleus)
Antinociceptive system
Analgesic
Smooth musculature stomach bowel → spastic constipation
Antidiarrheal
Ureter bladder bladder sphincter
Pain sensation
Analgesic
Mood alertness
Respiratory center Cough center
Antitussive

Opioid Analgesics: Side Effects

- Euphoria
- CNS depression
- Nausea and vomiting
- Respiratory depression
- Urinary retention
- Diaphoresis and flushing
- Pupil constriction (miosis)
- Constipation
- Itching

Repeated use of Morphine

- Psychological dependence
- Physical dependence
- Tolerance
- Withdrawal syndrome
- Hyperalgesia???????

Tolerance/Dependence/Addiction

- **Tolerance**

– Physiologic phenomenon resulting in progressive decline in potency of an opioid with continued use.

Dependence

– Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy.

- Abstinence syndrome
- Independent of tolerance

Addiction

– Psychological & behavioralsyndrome manifested by drug seeking behavior, loss of control o drug use, and continued us despite adverse effects.

Tolerance and Dependence

Withdrawl Reactions

Acute Action

- Analgesia
- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Flushed and warm skin

Withdrawl Sign

- Pain and irritability
- Hyperventilation
- Dysphoria and depression
- Restlessness and insomnia
- Fearfulness
- Increased blood pressure
- Diarrhea
- Pupillary dilation
- Hyperthermia
- Lacrimation, runny nose
- Chilliness and “gooseflesh”

Pregnancy and elderly

- If acetaminophen is insufficient, opioids are considered
- acceptable during pregnancy provided they are given for a short duration.
- Chronic opioid use can result in fetal dependence, premature delivery and growth retardation.
- In elderly

Opioid analgesics have an increased likelihood of more profound adverse effects as well as prolonged durations of action. Therefore it is best not to select an opioid.

If it is necessary, reduced doses must be utilized.

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
Strong opioid agonists				
Morphine Methadone Fentanyl	Strong -receptor agonists	Analgesia relief of anxiety sedation slowed gastrointestinal transit	Severe pain adjunct in anesthesia (fentanyl, morphine) pulmonary edema (morphine only) maintenance in rehabilitation programs (methadone only)	First-pass effect duration 1–4 h except methadone, 4–6 h *Toxicity:* Respiratory depression severe constipation addiction liability convulsions
Hydromorphone, oxymorphone: Like morphine in efficacy, but higher potency				
Meperidine: Strong agonist with anticholinergic effects				
Sufentanil, alfentanil, remifentanil: Like fentanyl but shorter durations of action				
Partial agonists				
Codeine	Less efficacious than morphine	Like strong agonists weaker effects	Mild-moderate pain cough	Like strong agonists, toxicity dependent on genetic variation of metabolism

Opioids

- Weak opioids
  - Codeine
  - Tramadol
- Strong opioids
  - Oxycodone
  - Morphine
  - Methadone
  - Fentanyl
  - Mepiridine

Morphine

- **Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, morphine may be used to supplement the sleep-inducing properties of hypnotic agents**

- **Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscles**

- **Morphine produce a powerful sense of euphoria and well-being.**

- **Morphine is also used in the treatment of acute pulmonary edema, intravenous morphine is dramatically relieve dyspnea cause by pulmonary edema associated with left ventricular failure.**

Kidney

Morphine has 2 biologically active metabolites, morphine-6-glucuronide and morphine-3-glucuronide.

Morphine-6-glucuronide binds to the opioid receptor and is believed to contribute to the effects of the parent compound. Morphine-3-glucuronide does not bind to the receptor and is believed to contribute in some cases to adverse effects such as myoclonus and confusion.

Usually, the metabolites are considered a clinical issue only when their concentrations in the blood are likely to fluctuate differently than the concentration of the parent compound. This can occur during renal insufficiency,

Hydromorphone

- may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulation.

(Mepiridine, pethidine)

- Repetitive dosing leads to accumulation of the toxic metabolite normeperidine (normeperidine)

- Norpethidine accumulation causes
  - CNS hyper-excitability, subtle mood changes,

  Tremors, Multifocal myoclonus, Seizures

- Common with repeated large doses, eg 250 mg per day.

- It is renally cleared, and use of meperidine in patients with kidney disease is not recommended .

Mepiridine

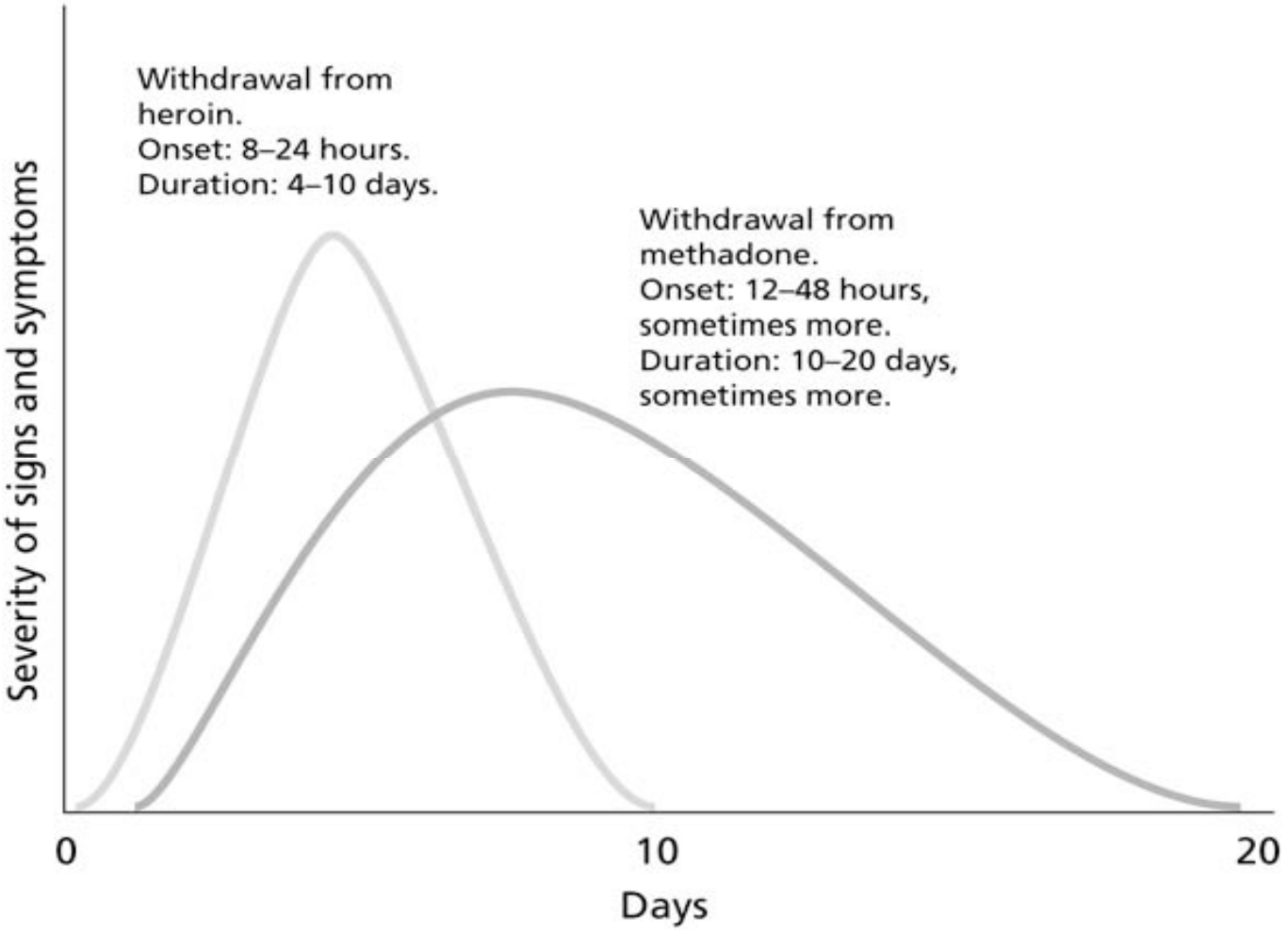
- Obstetric labor
- Shivering

Methadone

- NMDA receptors blocking
- Monoaminergic reuptake transporters.
- Treat difficult to treat pain, especially when morphine failed.
- Widely used in opioids abuse.

why?????

Course of opioid withdrawal



Source: NSW Department of Health (2007) NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines

Tramadol

- Analgesic action mechanism
  - Not fully understood
  - Weak affinity for μ-opioid receptor
  - Inhibition of norepinephrine reuptake

    → α2-adrenoreceptor activation

    → act synergistically with tramadol's opioid receptor activation

    → analgesia
- Advantage
  - Less respiratorpsychomotor recoveryy depression, nausea, vomiting, constipation
  - Rapid
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

Peripherally Acting Opioid

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist
    → analgesia without CNS side effect
- Loperamide
  - μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia
  - Relieve diarrhea

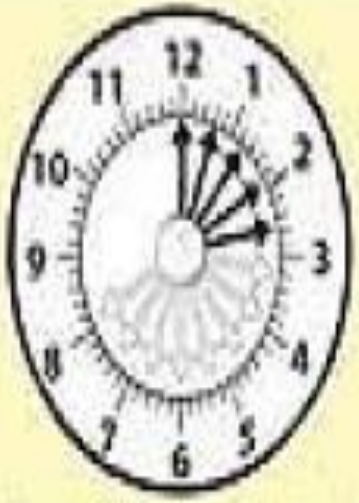
Anxiolytic and Hypnotic drugs

- **Anxiety is unpleasant state of tension and fear that seems to arise from unknown source.**
- **The symptoms of severe anxiety are similar to those of fear (such as tachycardia, palpitation) and involve sympathetic activation.**
- **Sever anxiety may be treated with antianxiety drugs and/or some form of behavioral and psychotherapy.**
- **Because all of the antianxiety drugs also cause sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) .**

Benzodiazepines

- **Are the most widely used anxiolytic drugs.**
- **have largely replaced barbiturates because they are safer and more effective.**

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

Long-acting	Intermediate-acting	Short-acting
	 10–20 Hours	 3–8 Hours
Clorazepate *Chlordiazepoxide* *Diazepam* *Flurazepam* *Quazepam*	*Alprazolam* *Estazolam* *Lorazepam* *Temazepam*	*Oxazepam* *Triazolam*

- **MOA:**

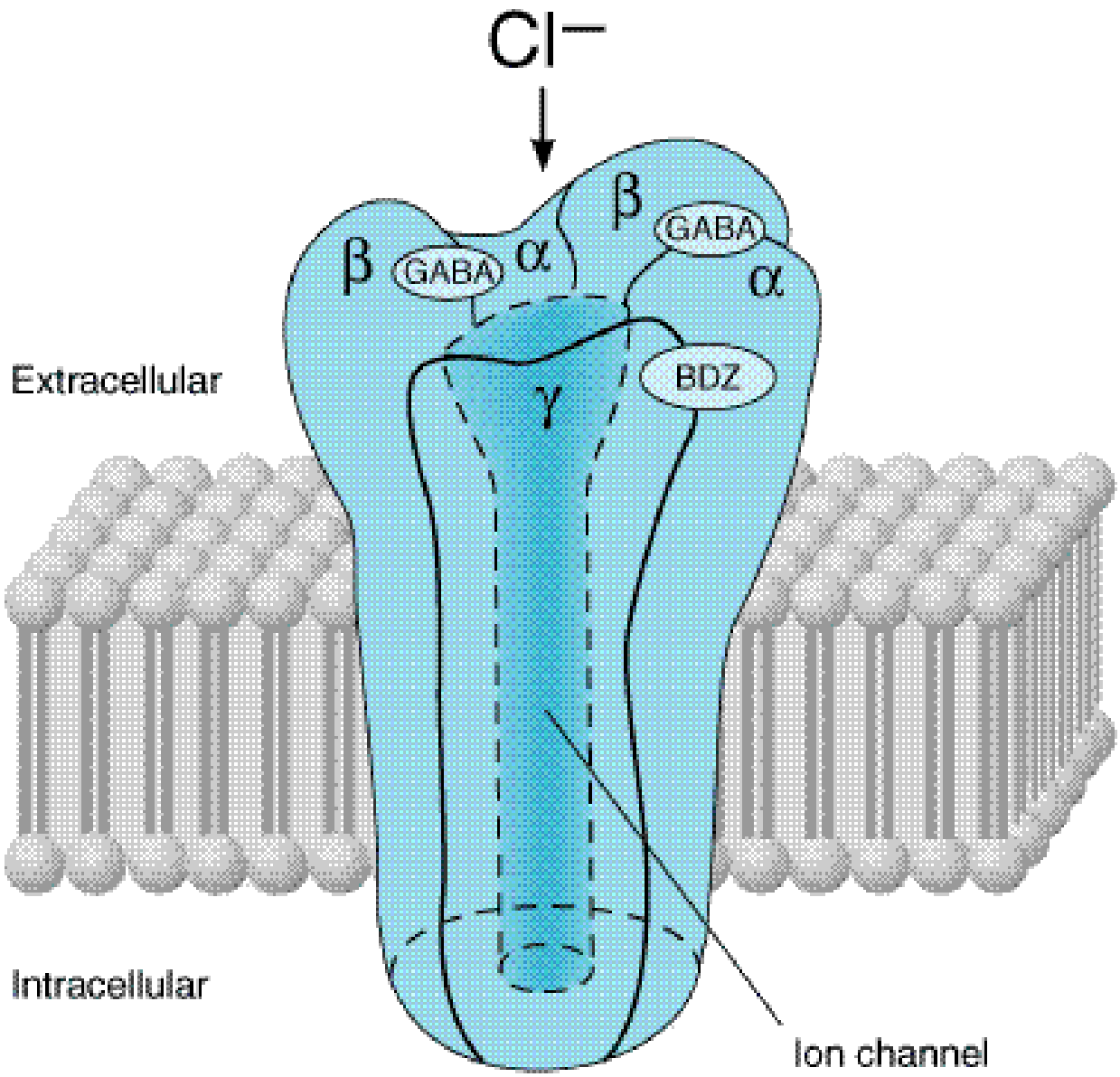
  Benzodiazepines enhances the affinity of GABA receptors for gamm-aminobutyric acid (GABA) receptors.

  GABA is the major inhibitory neurotransmitter in the CNS.

- **Binding of GABA to its receptors triggers the opening of chloride channel, which leads to an increase in the chloride conductance.**

- **The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and thus inhibits the formation of action potentials.**

- **Benzodiazepines bind to GABA receptors resulting in a more frequent opening of adjacent chloride channels specific, high affinity sites on the cell membrane, which are separate from but adjacent to the receptor for GABA.**


Cl−
β
GABA
α
β
GABA
α
γ
BDZ
Extracellular
Intracellular
Ion channel

Benzodiazepines

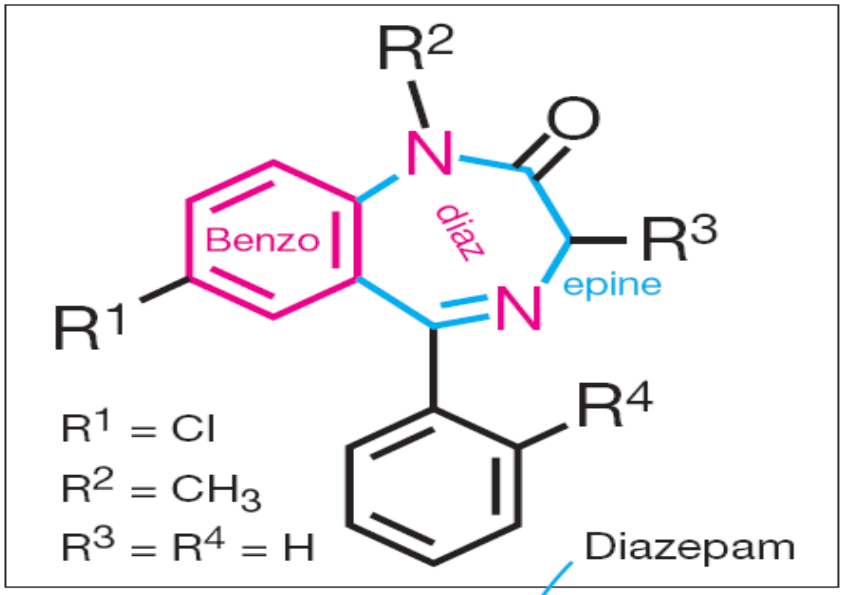
- They do not have analgesic action nor antipsychotic, but they exhibit the following actions:

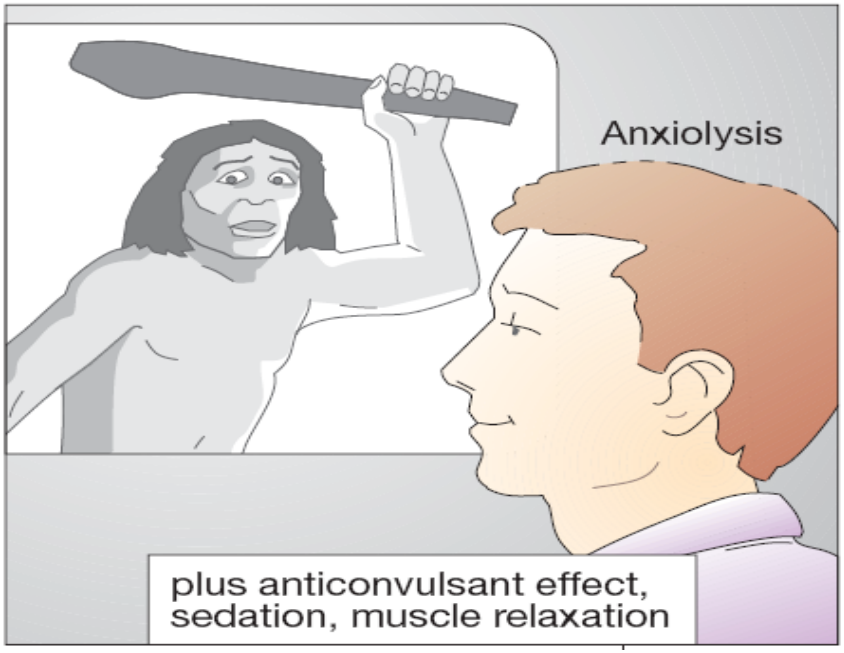
A. Reduction of anxiety (anxiolytic), at low doses.

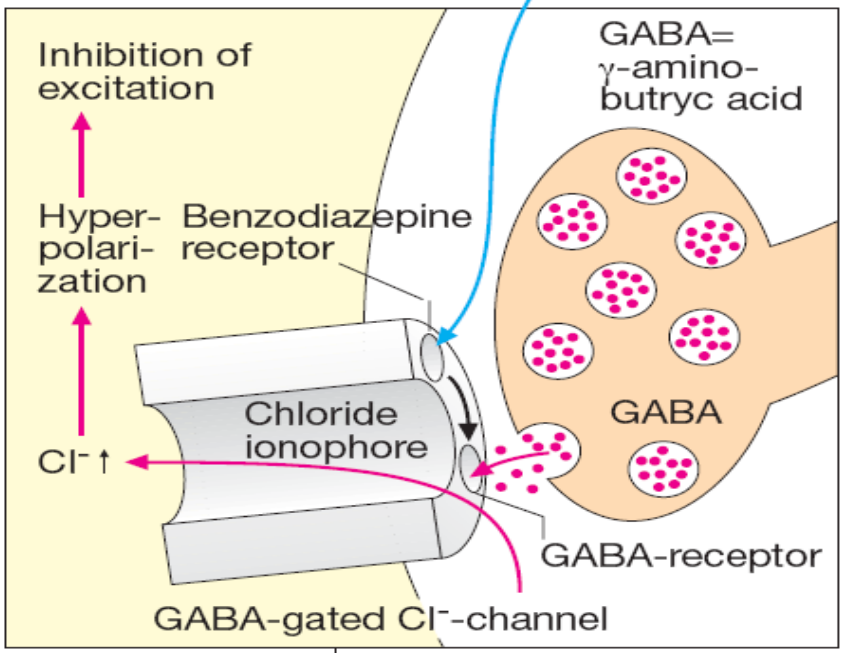
They are useful in treating the anxiety that accompanies some form of depression and schizophrenia.

These agents should not be used to alleviate the normal stress of everyday life, and should be reserved to sever anxiety.

Should be used for short periods of time because of the addiction potential.







- **The longer acting benzodiazepines, such as Diazepam, are preferred with anxiety that may require treatment for prolonged periods of time.**

- **The anti-anxiety effects of the Benzodiazepines is less subject to tolerance than the sedative and hypnotic effects.**

- **Tolerance is decreased responsiveness to repeated doses of drug-occur when used for more than one to two weeks.**

  cross tolerance exists among this group of agents and has been associated with a decrease in GABA receptors density.

B. **Muscular relaxant: at high doses relax the spasticity of skeletal muscles probably by increasing presynaptic inhibition in the spinal cord.**

Diazepam is useful in the treating a muscle spasm such as occur in muscle strain, and in treating spasticity from degenerative disorder such as multiple sclerosis.

C. Sedative and hypnotic: all Benzodiazepines used to treat anxiety have some sedative properties and some can produce hypnosis. However, not all are useful as hypnotic agents.

It is important to balance the sedative effect needed at bedtime with the residual sedation (hangover) on awakening.

The three most commonly prescribed for sleep disorder are long-acting Flurazepam, intermediate-acting Temazepam, and short-acting Triazolam.

hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

CATEGORIES OF INSOMNIA

Transient insomnia	Short-term insomnia	Long-term insomnia
•**Lasts <3 days** •---Caused by a brief environmental or situational stressor. •---Respond to attention to sleep hygiene rules. •--- Hypnotics should be used at the lowest dose and for only 2-3 nights.	•**3 days to 3 weeks** •--- Caused by a personal stressor such as illness, grief, or job problems. •---Sleep hygiene education is the first step. •---Hypnotics may be used adjunctively for 7-10 nights. •---- Hypnotics are best used intermittently during this time, with the patient skipping a dose after 1-2 nights of good sleep.	•**lasted for >3 weeks** •**---N**o specific stressor may be identifiable. •---A more complete medical evaluation is necessary in these patients, but most do not need an all-night sleep study.

PK criteria

Long-acting compounds (e.g. flurazepam) may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover

Short-acting compounds (e.g. triazolam) avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety

LONG-TERM INSOMNIA

Nonpharmacological treatments are important for all patients with long-term insomnia.These include

- Reduced caffeine intake
- Avoidance of alcohol
- Adequate exercise
- Relaxation training
- Behavioral-modification approaches, such as sleep-restriction and stimulus-control therapies.
- Nonpharmacological treatments for insomnia have been found to be particularly effective in reducing sleep-onset latency and time awake after sleep onset.

D. **Anticonvulsant: several Benzodiazepines have anticonvulsant activity and used to treat epilepsy and other seizure disorder.**

Clonazepam is useful chronic treatment of epilepsy, whereas diazepam is the drug of choice in terminating grand-mal epileptic seizers.

E. **Anterograde amnesia: Benzodiazepines does produce temporary impairment of memory.**

The short –acting agents are employed in premedication for endoscopic and bronchoscopic procedures such as angioplasty.

Benzodiazepines

- **Adverse effect:**

  (1) Drowsiness and confusion: the two most common side effects.

  (2) Ataxia occurs at high doses and precludes activities that require fine motor coordination.

  (3) Cognitive impairment, can occur .

  (4) Triazolam often shows rapid development of tolerance, early morning insomnia, daytime anxiety.

- **Interaction and precautions:**

  (1) Used cautiously in treating patient with liver diseases.

  (2) Should be avoid with acute narrow angle glaucoma.

  (3) Alcohol and other CNS depressant enhance the sedative-hypnotic effect.

Benzodiazepines

- **Physiological and physical dependence can developed if high doses of the drug are given over a prolonged period.**
- **Sudden withdrawal of benzodiazepines results in withdrawal symptoms, and tension.**
- **Benzodiazepine withdrawal syndrome is caused by stopping benzodiazepines or during dosage reduction.**
- **Because of the long half-lives of some of the Benzodiazepine withdrawal symptoms may not occur until a number of days after discontinuation of therapy**
- **Withdrawal symptoms including confusion, anxiety, agitation, insomnia, and tension.**
- **Over dose**

Flumazenil is the only benzodiazepine receptor antagonist available for clinical use. The drug is available by IV administration only. Onset is rapid but duration is short, with a half-life of about one hour.

New Benzodiazepine Receptor Agonists

- **An hypnotic agent that act on the same receptors as benzodiazepines. Nonetheless, it has no anticonvulsant effect nor muscle relaxation.**

- **It shows minimal withdrawal effects and little or no tolerance effect occur with prolonged use.**

- **Currently it is the most frequently prescribed hypnotic drug in the United States.**

- **Although zolpidem potentially has advantages over the benzodiazepines, clinical experience with the drug is still limited.**

- **Adverse effects includes nightmares, agitation, headache, daytime drowsiness.**

ZALEPLON

- Its plasma **$t_{1/2}$ is ~1 hours**

- **approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime.**

ZOLPIDEM

- Its plasma **$t_{1/2}$ is ~2 hours**

- **Cover most of a typical 8-hour sleep period, and is presently approved for bedtime use only.**

Novel Benzodiazepine Receptor Agonists

- Zaleplon and zolpidem are **effective in relieving sleep-onset insomnia**. Both drugs have been approved by the FDA for use for up to **7-10 days** at a time.

- Zaleplon and zolpidem **have sustained hypnotic efficacy** without occurrence of rebound insomnia on abrupt discontinuation.

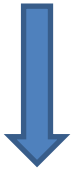
MELATONIN CONGENERS

RAMELTEON

- Synthetic tricyclic analog of **MELATONIN**.
- It was approved for the treatment of insomnia, specifically sleep onset difficulties.

MECHANISM OF ACTION

- Melatonin levels in the suprachiastmatic nucleus rise and fall in a circadian fashion



concentrations increasing in the evening as an individual prepares for sleep, and then reaching a plateau and ultimately decreasing as the night progresses.

MELATONIN CONGENERS

Mechanism of Action

- Two **GPCRs** for melatonin, **MT_1** and **MT_2,** are found in the suprachiasmatic nucleus, each playing a different role in sleep.
- **RAMELTEON** binds to both **MT_1** and **MT_2** receptors with high affinity.
- Binding of **Melatonin** to **MT_1** receptors **promotes the onset of sleep**.
- Binding of **Melatonin** to **MT_2** receptors shifts the timing of the circadian system.
- **RAMELTEON** is efficacious in combating both transient and chronic insomnia

Buspirone

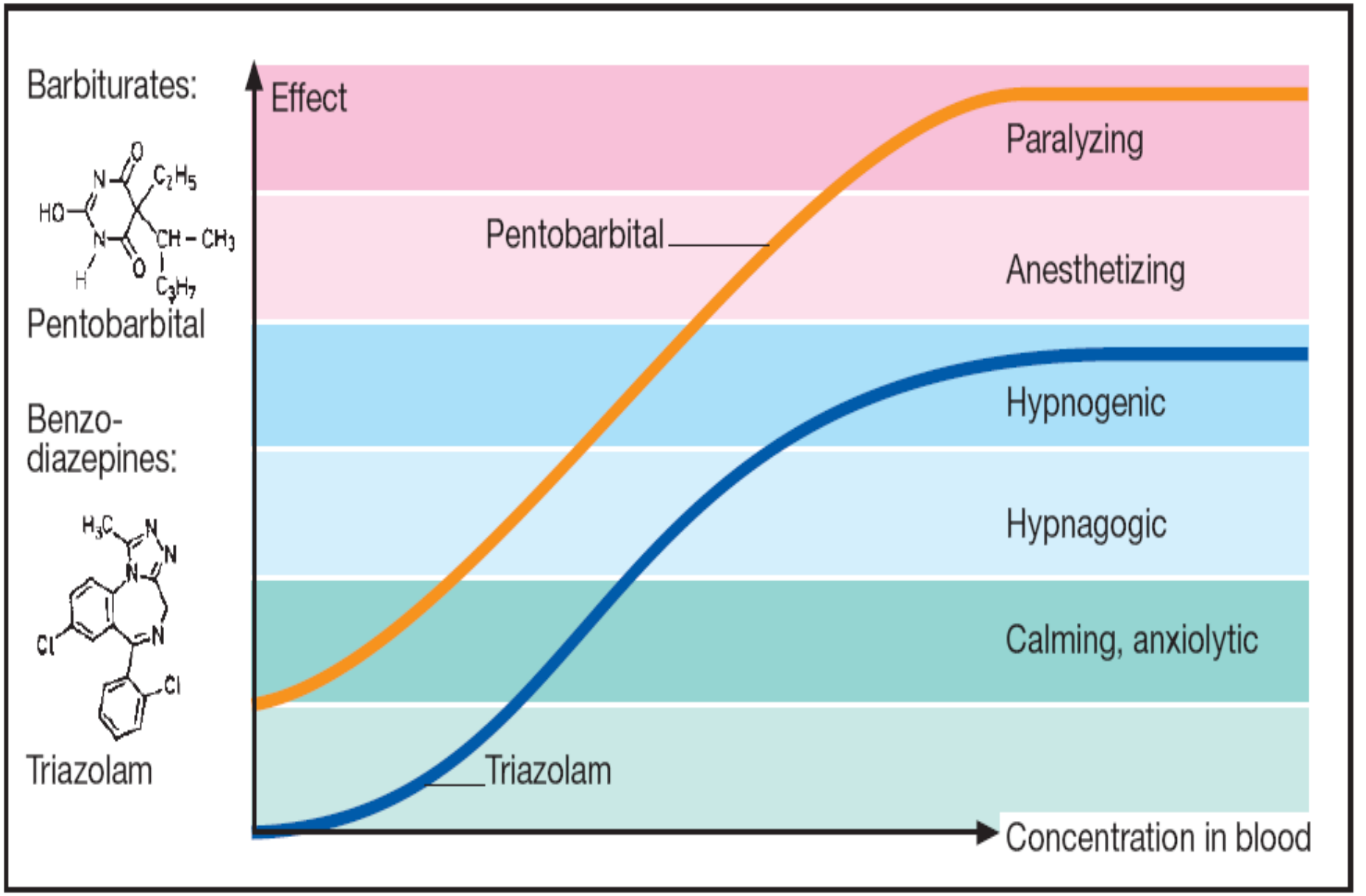
- **Is useful in treatment of generalized anxiety disorders, and has efficacy comparable to benzodiazepines.**
- **Its action is mainly mediated by serotonin (5HT) receptors.**
- **The anxiolytic effects of buspirone may take more than a week to become established, making the drug unsuitable for management of acute anxiety states (not very effective in panic disorders).**
- **buspirone lacks anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.**
- **The frequency of adverse effects is low, the most common effects being headaches, dizziness, nervousness.**

Barbiturates

- **The Barbiturates were formally the mainstay of the treatment used to sedate the patient or to induce and maintain sleep.**

- **Today they have been largely replaced by the benzodiazepines because they induce tolerance, physical dependence and very severe withdrawal symptoms, and most importantly, their ability to cause coma in toxic doses.**

- **Short acting barbiturates such as Thiopental is still used to induced anesthesia.**



C. Concentration dependence of barbiturate and benzodiazepine effects

Barbiturates

- They exert their action by binding to GABA receptors and so potentiate the GABA action on the chloride channel opening (prolonging the opening duration). The binding site is distinct from that of benzodiazepines.

  In addition they can block excitatory glutamate receptors.
- Their action summarized in:

A. Depression of the CNS: at low doses they produce sedation, and high doses they cause hypnosis.

   thus it is useful as anesthetic. The selection of barbiturate is strongly influenced by the desired duration of action.

   The ultra short barbiturate such as thiopental are used intravenously to induce anesthesia.

Barbiturates

B. Anticonvulsant: Phenobarbital (long-acting) is used in long-term management of tonic-clonic seizures, status epilepticus.

Phenobarbital has been regarded as the drug of choice for treatment of young children with febrile seizure.

However, it can depress cognitive performance in children and the drug should be used cautiously.

C. Anxiety: barbiturates have been used as mild sedative to relieve anxiety, nervous tension and insomnia. (replaced by benzodiazepines).

Adverse effects and interactions

a. **Respiratory depression: they suppress the hypoxic receptors that response to CO2, and overdosage is followed by respiratory depression and death.**

for many decades, barbiturates poisoning has been a leading cause of death among drug overdose.

b. **Enzyme induction: they induce the CYP450 microsomal enzymes in the liver, and thus interact with many drugs.**

c. **CNS effects: cause drowsiness, impaired concentration.**

d. **Drug hangover: hypnotic doses produce a feeling of tiredness after patient awake (many hours).**

e. **Physical dependence: sudden withdrawal may cause tremors and anxiety and weakness**

Features of withdrawal and dependence vary. Commonly there is a kind of **psychological dependence** based on the fact that the treatment works to reduce patients' anxiety or sleep disturbance and therefore they are unwilling to stop. If they do stop, there can be relapse, where original symptoms return.

Withdrawal of BDZs should be gradual after as little as 3 weeks' use but for long-term users it should be very slow, e.g. about 6–12 weeks. Withdrawal should be slowed if marked symptoms occur and it may be useful to substitute a long $t_{1/2}$ drug (e.g. diazepam) to minimize rapid fluctuations in plasma concentrations. **In difficult cases withdrawal may be assisted by concomitant use of an antidepressant.**

Dosages of drugs used commonly for sedation and hypnosis

Sedation		Hypnosis	
Drug	**Dosage**	**Drug**	**Dosage (at Bedtime)**
Alprazolam (Xanax)	0.25-0.5 mg 2-3 times daily	Chloral hydrate	500-1000 mg
Buspirone (BuSpar)	5-10 mg 2-3 times daily	Estazolam (ProSom)	0.5-2 mg
Chlordiazepoxide (Librium)	10-20 mg 2-3 times daily	Eszopiclone (Lunesta)	1-3 mg
Clorazepate (Tranxene)	5-7.5 mg twice daily	Lorazepam (Ativan)	2-4 mg
Diazepam (Valium)	5 mg twice daily	Quazepam (Doral)	7.5-15 mg
Halazepam (Paxipam)	20-40 mg 3-4 times daily	Secobarbital	100-200 mg
Lorazepam (Ativan)	1-2 mg once or twice daily	Temazepam (Restoril)	7.5-30 mg
Oxazepam	15-30 mg 3-4 times daily	Triazolam (Halcion)	0.125-0.5 mg
Phenobarbital	15-30 mg 2-3 times daily	Zaleplon (Sonata)	5-20 mg
		Zolpidem (Ambien)	5-10 mg

Sedative/Hypnotics

All of the anxiolytics/sedative/hypnotics should be used only for symptomatic relief.

****

All the drugs used alter the normal sleep cycle and should be administered only for days or weeks, never for months.

****

USE FOR

SHORT-TERM TREATMENT

ONLY!!