



S O U T H W E S T O H I O  
**PAIN INSTITUTE**

Patient Care Education Research

# Pharmacology of Pain Management

Muhammad A. Munir, MD

Diplomat American Board of Anesthesiology and Pain  
Management

# Objectives

- Review pharmacology of non-opioid and opioid analgesics used in pain medicine
- To tell you everything that you need to know about pharmacotherapy for pain

# *Real Objectives*

- To make you realize that pharmacology of general anesthetics is not as horrible as you may think (provides you comparison)
- To test if you can stay awake despite having to attend a very boring topic!!

# A patient's perspective

- **“My dream is for a medication that can relieve my pain while leaving me alert and with no side effects.”**
- **Panel member, Agency of health care policy and Research,AHCPR(1991-1992)**

# WHO Analgesic step ladder

- **Step 1: Non opioid (+ or-) adjuvant.(VAS 2-4/10).**
- **Step 2: Weak opioid (+) Non opioid (+ or-) adjuvant(VAS 4-6/10).**
- **Step 3: Strong opioid(+ ) Non opioid (+ or-) adjuvant(VAS>6/10).**
- **Step 4: Anesthetic/Neurosurgical Interventions.**

# Golden rules

- **Pharmacodynamics**  
Mechanism of action, Systemic effects of the drug.
- **Pharmacokinetics**  
Absorption, Distribution, Metabolism and excretion.
- **Drug interactions**
- **Adverse reactions, side effects, and genuine allergies.**

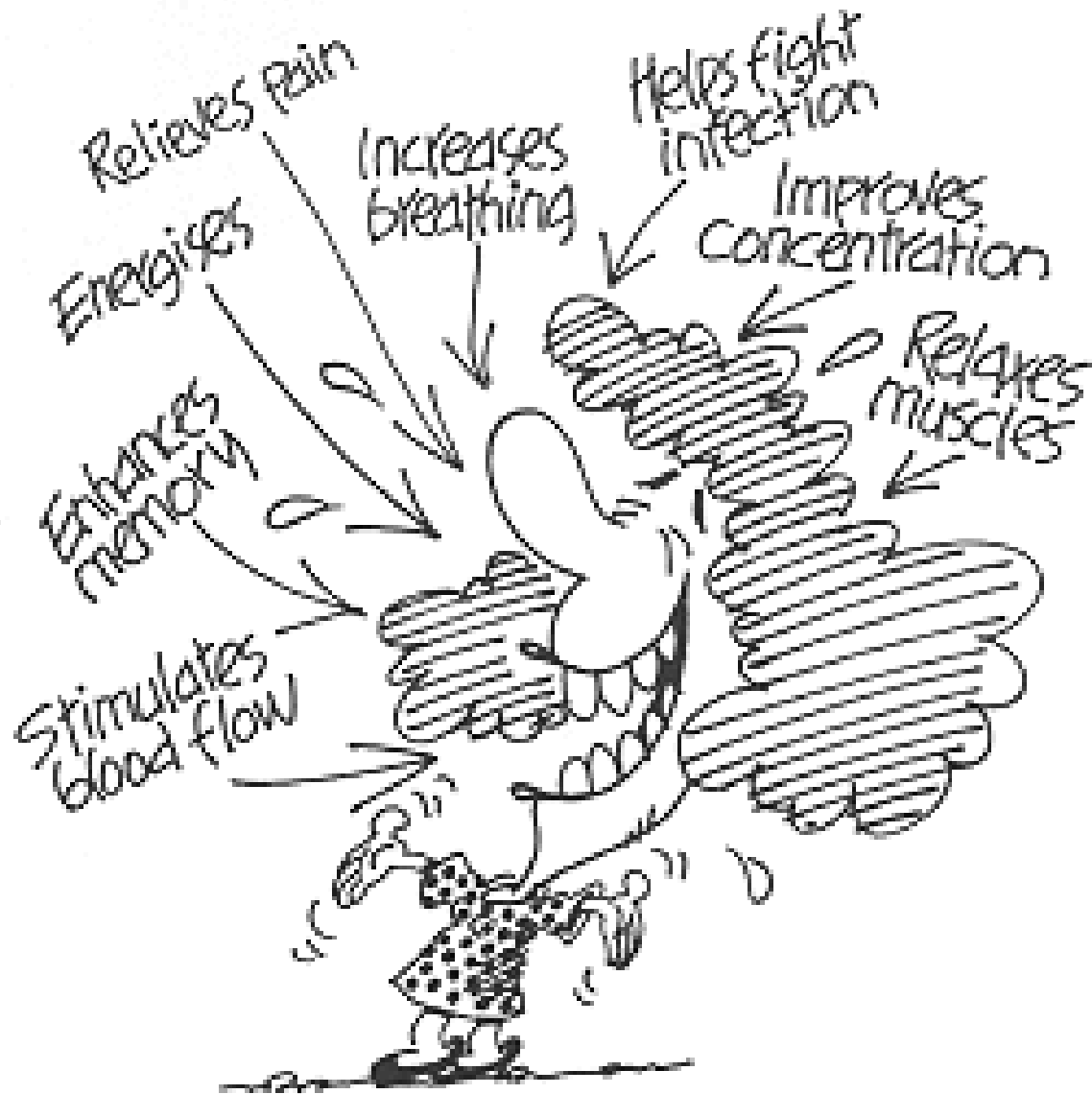
# Adjuvant medications

- **Antidepressants.**
- **Anticonvulsants.**
- **Neuroleptic agents.**
- **Antiarrhythmic drugs.**
- **Corticosteroids.**
- **Osteoclast inhibiting medications.**
- **Spasmolytics.**
- **Alpha blockers.**
- **Alpha 2 agonists.**

# Adjuvant medications

- **Adjuvant analgesics differ from Opioid analgesics in important conceptual ways:**
  - **Adjuvants may or may not elicit pain relief.**
  - **The nature of the dose/response relationship is not predictable.**
  - **They are mainly useful in Neuropathic pain.**





# Antidepressants for Chronic Pain

- **Antidepressants** increase the extraneuronal concentrations of **Norepinephrine and Serotonin**, which are responsible for modulating pain.
- The neurotransmitter Serotonin is released by a major descending inhibitory pathway that arises in the **Periaqueductal gray** region of the midbrain. The **Noradrenergic** pathway is a major descending pathway. It arises in the **Locus Ceruleus** of the pons.

# Insight on Neurotransmitters

- **Norepinephrine**
- **Serotonin**
- **Dopamine**
- **Alertness and energy**
- **Obsessions and compulsions**
- **Attention and motivation**

# Insight on Neurotransmitters

- **Norepinephrine**
- **Serotonin**
- **Dopamine**
- **Tremors, tachycardia and erectile dysfunction.**
- **Sexual dysfunction and sleep disturbances.**
- **Psychomotor activation and aggravation of Psychosis.**

# Antidepressants with NE & 5HT Activity

- TCAs (NE > 5HT)
  - amitriptyline
  - imipramine
  - desipramine
  - nortriptyline
- SSRIs (5HT > NE)
  - Citalopram and escitalopram
  - paroxetine
  - fluoxetine
  - sertraline
- SNRIs (? NE = 5HT)
  - bupropion
    - dopaminergic
  - venlafaxine
    - dopaminergic
  - mirtazapine
    - Alpha-adrenergic
  - fluvoxamine
  - duloxetine

# Monoamine Oxide Inhibitors

- Monoamine oxidase [MAO] is a mitochondrial enzyme, the function of which is to accomplish the oxidative deamination of endogenous monoamines.
- The enzyme is directed at two receptor subtypes, MAO-A and MAO-B, on the basis of the affinity of each of these enzymes for specific amine substrates. Monoamine oxidase inhibitors most commonly used in psychiatry are **Phenelzine** (**Nardil**) and **Tranylcypromine** (**Parnate**).

# Drug interactions of MAOI

- Serotonin syndrome when MAOI interact with **Dextromethorphan**, **SSRIs**, **Venlafaxine** and **Meperidine**.
- Adverse Depressive drug interactions has been described with **Fentanyl** secondary to accumulation of the opioid ,which produces respiratory depression,hypotension and coma.

# **Serotonin syndrome**

- **Change in mental status**
- **Hyperreflexia**
- **myoclonus,tremors**
- **Diaphoresis,**
- **Hyperthermia ,Diarrhea**
- **Rhabdomyolysis**
- **Seizures**
- **DIC**
- **Hypertension**
- **Tachycardia**
- **Ventricular arrhythmias**
- **Mortality**



# Treatment

- Supportive care
  - Cooling
  - Fluids
  - Electrolytes
- Medications
  - Cyproheptadine
  - Bezodiazpines
  - Propranolol
  - Methysergide

# Heterocyclic Antidepressants

- **Acute synaptic effects of polycyclic antidepressants that may be related to the therapeutic activity include Norepinephrine and Serotonin reuptake blockade, Serotonin 1-A receptor agonism.**
- **In addition, receptor-related major side effects such as Anticholinergic (Dry mouth, Tachycardia) H1-receptor antagonism (sedation), alpha receptor modulation (Hypotension, Priapism) and D2 receptor antagonism (Extrapyramidal SX).**

# Heterocyclic Antidepressants

- **Tertiary amines**
- **Amitryptilline**(Elavil)
- **Doxepin**(Sinequan)
- **Imipramine**(Tofranil)
- **Secondary amines**
- **Amoxapine**(Asendin)
- **Desipramine**(Norpramin)
- **Nortryptilline**(Pamelor)

# Heterocyclic Antidepressants

- Triazolopyridine: **Trazdone** (**Desyrel**)
- Phenylpiperazine: **Nefazdone** (**Serozone**) both have mCPP (meta-chlorophenylpiperazine) metabolite, mCPP has dual mechanism of action 5HT<sub>1</sub> agonist and 5HT<sub>2</sub> /5HT<sub>3</sub> antagonist
- AminoKetone: **Bupropion** (**Wellbutrin**) inhibit the reuptake of NE and Dopamine.
- Phenethylamine: **Venlafaxine** (**Effexor**) inhibit the reuptake of 5HT, NE and Dopamine.

# Serotonin- selective Reuptake inhibitors

- **Fluoxetine**(Prozac) -**Sertraline**(Zoloft)
- **fluvoxamine**(Luvox)- **Paroxetine**(Paxil)
- **SSRIs differ in their respective receptor -specific side-effect profiles,existence of active metabolites and inhibition of Hepatic isoenzymes (CYP 450).**
- **Adverse effects include HA, insomnia, nervousness,tremors,n/v, diarrhea, anorexia and ejaculatory dysfunction.**

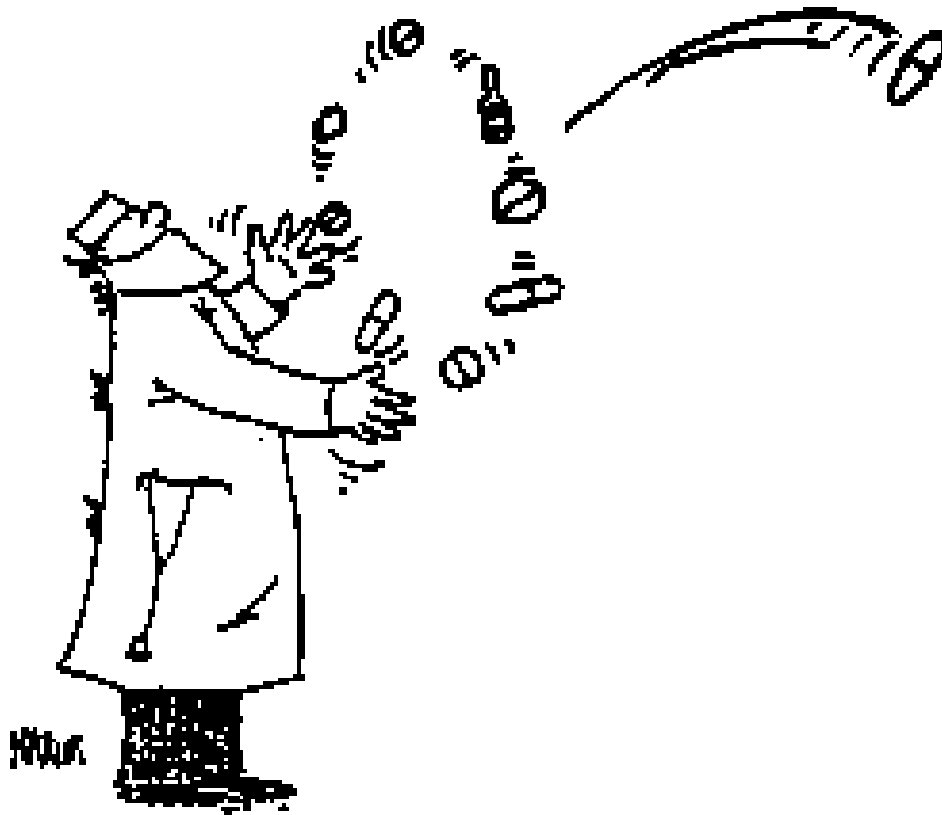
# Cytochrome P-450

- At least 34 enzymes has been identified in humans,CYP 2D6 is deficient in 8%.
- CYP 1A2 metabolizes Butyrophenones.
- CYP II C metabolizes **Phenytoin** , **Warfarin** and **Diazepam**.
- CYP II D6 metabolizes **Amitriptyline** , **Nortriptyline** , **Dextromthorphan** and **Chlopromazine**.
- CYP III A4 metabolizes **Alprazolam**, **Triazolam** **Midazolam** , **Lidocaine** and **Carbamazepine**.

# Hepatic enzyme inducers and inhibitors

- **Inhibitors**
- **Erythromycin, Ethanol(acute), Isoniazide, Cimetidine, Omeprazole, Propranolol , Valproic acid, TMP/SMX, Propoxyphene and SSRIs.**
- **Inducers**
- **Phenytoin, Barbiturates, Carbamazepine, Ethanol (chronic), Rifampin.**

# Pharmacological Therapy





# Anticonvulsants

- Sodium Channel Antagonists
  - carbamazepine, lamotrigine, oxcarbazepine, phenytoin, topiramate, zonisamide
- Calcium Channel Antagonists
  - ethosuximide, gabapentin, lamotrigine, topiramate, valproate, zonisamide, pregabalin
- GABA modulation
  - gabapentin, phenobarbital, tiagabine, topiramate, valproate, zonisamide
- Glutamate antagonists
  - topiramate, felbamate

# Carbamazepine(Tegretol)

- Similar structure to Heterocyclics
- Substantial increases in the clearance occur secondary to hepatic enzyme autoinduction.
- Use of metabolite **Oxcarbamzpine** may be a new therapeutic modality.
- Side effects include Dizziness, Gait disturbance,n/v , Hepatic dysfunction and neutropenia.

# Gabapentin (Neurontin)

- **Gabapentin** is amino acid analogue of GABA without GABA mimetic activity.
- Mechanism of action could be related to inhibition of Glutamate synthesis or Ca<sup>+</sup> channel blockade.
- It is primarily eliminated through the kidney .
- The drug has a low toxicity and causes no significant drug interaction.
- Side effects include somnolence, fatigue, dizziness, ataxia , diplopia and tremors.

# Clonazepam(Klonopin)

- **A Benzodiazepine, may be useful in management of Neuropathic pain.**
- **Side effects reported include:  
drowsiness,dizziness,hypersalivation, speech disturbance,,ataxia,hypotension, behavioral alterations,and skeletal muscle relaxation.**

# Phenytoin

- **Phenytoin(Dilantin)** Inactivates sodium channels. Side effects of **Phenytoin** are nausea, vomiting, rash, Stevens-Johnson syndrome, SLE, PAN (polyarteritis nodosa), elevated LFTs, reduced CBC and generalized lymphadenopathy.

# Valproic acid

- **Valproate**(Depakote) is associated with increases of GABA levels in the CNS. Side effects include liver toxicity, decreased platelets ,drowsiness and ataxia. Transient GI effects include n/v, diarrhea, and abdominal cramps.
- Used as preventive therapy for Migraine and Cluster headaches.

# Lamotrigine

- **Lamotrigine (Lamictal)** is a sodium channel blocker, may cause rash, dizziness, ataxia, headache and inhibition of Dihydrofolate Reductase.

# Topiramate

- **Topiramate** (**Topomax**) an AMPA receptor blocker, may cause sedation, ataxia, headache inhibition of carbonic anhydrase and nephrolithiasis.



# Evidenced-Based Medicine

<b>Antidepressant</b>	<b>NNT</b>
TCA (balanced)	2.7
TCA (selective noradrenergic)	2.5
SSRI	6.7
Anticonvulsants (Na)	2.5
Anticonvulsants (Ca)	4.1



**MATZ'S RULE  
REGARDING  
MEDICATIONS:**

A drug is that substance which,  
when injected into a rat,  
will produce a scientific report.

# Azapirones

- **Buspirone** (**Buspar**) is a selective 5 HT 1A partial agonist.
- Used as an anxiolytic ,has no sedative , depressant effects nor abuse potential.
- Not used as prn medication.
- Side effects include dizziness ,nausea, headaches and insomnia.

# Benzodiazepines

- They exert their therapeutic effects by binding to GABA A receptor.
- In vitro studies demonstrate BZ 1 receptor is associated with sedation, unlike BZ 2, which is associated with anticonvulsant, anxiolytic, myorelaxant and amnestic properties.
- Anatomically GABA receptors are exclusively present in the Central nervous system.

# Bezodiazpines

- Midazolam(versed)
- Triazolam(Halcion)
- Flurazepam(Dalmane)
- Chlordiazepoxide(Librium)
- Lorazepam(Ativan)
- Temazepam(Restoril)
- Oxazepam(Serax)
- Alprazolam(Xanax)
- Diazepam(valium)

# Benzodiazepines

- High lipid solubility of **Diazepam** facilitates its efficient absorption after oral administration and rapid entry to CNS and its rapid distribution to inactive tissue sites.
- Metabolism of **Diazepam** in the liver results in active metabolites (Desmethyl diazepam) which is slightly less potent than Diazepam.
- **Lorazepam** , **Oxazepam** and **Midazolam** are metabolized mainly by conjugation.

# Imidazopyridine

- **Zolpidem** (**Ambien**) is highly selective BZ 1 agonist.
- Avoids major side effects such as amnesia.
- Mainly indicated for sleep is not in the treatment of patients for whom muscle relaxation are not patient specific needs.
- **Zolpidem** is not removed by hemodialysis, and no accumulation of the drug appears after 21 days.

# Drugs enhancing GABA inhibition

- Benzodiazepines (increased affinity)
- Volatile Anesthetics , **Barbiturates** , **Etomidate** **Propofol**, (Keep the Cl channel open for longer duration of time)
- Alpha agonists (enhance release)
- Volatile Anesthetics and **Valproic acid**(Inhibit disposal)



# Clinical Uses

- Painful episodes associated with high degree of anxiety
- Skeletal muscle relaxation
- Preoperative medication
- Intravenous sedation
- Induction of Anesthesia
- Anticonvulsant
- Delirium Tremens

# Anti-arrhythmic agents

- Lidocaine(Xylocaine)
- Tocainide(Tonocard)
- Phenytoin(Dilantin)
- Mexiletene(Mexitil)
- Propranolol(Inderal)
- Bretylium(Brtylol)
- Verapamil(Calan)
- Adenosine(Adenocard )

# Alpha adrenergic blockers

- **Phentolamine**(Regitine) (Diagnosis of SMP),act on alpha 1 and alpha 2 receptors.
- **Prazosin**(Minipress),**Doxazosin** (Cardura), and **Terazosin** (Hytrin) are alpha 1 receptor blockers.
- Adrenergic blocking agents are useful adjuncts in the treatment of SMP.

# Alpha 2 agonists

- **Clonidine**(Catapres) is believed to inhibit pain transmission by modulating Norepinephrine and 5HT release in the dorsal horn.
- Available in an oral dosage, transdermal and for epidural use.
- Sedation, xerostomia, constipation, orthostatic hypotension and Bradycardia. Abrupt withdrawal may lead to rebound HTN.
- Tricyclics reduce effectiveness.

# Alpha 2 agonists

- **Clonidine**(Catapress) is indicated in:
  - Neuropathic pain
  - Migraine prophylaxis
  - Detoxification
  - Supplementation of Analgesia
  - Hypertension

# NMDA antagonists

- **Dextromethorphan**(**Drixoral**)
- **Ketamine** (**Ketalar**)
- **Methadone**(**Dolophine**)
- **Amantadine**
  - NMDA antagonists are believed to inhibit pain transmission by blocking NMDA receptors. Prevent development of opioid tolerance and suppresses the development of wind-up phenomenon.

# Ketamine

- **Ketamine (Ketalar)** is a Phencyclidine derivative that produces Dissociative Anesthesia.
- Only the Racemic mixture is available for clinical use .
- Binds to Phenylcyclohexyl Piperidine(PCP) receptor which appears to be coupled with NMDA.
- Ketamine is metabolized extensively to Norketamine.

# Side effects of Ketamine

- **Increased Intracranial Pressure**
- **Sympathetic nervous system stimulation**
- **Salivary and tracheobronchial secretions**
- **Emergence Delirium**



# Spasmolytics

- Carisoprodol(Soma)
- Chlorzoxazone(Paraflex)
- Cyclobenzaprine(flaxeril)
- Methocarbamol(Robaxin)
- Orphenadrine(Norflex)
- Baclofen(Lioresal)
- Tizanidine(Zanaflex)
- Metaxalone (Skelaxin)
- Benzodiazpines

# Spasmolytics

- **Carisoprodol**(Soma), central-acting muscle relaxant,metabolized in liver to *Meprobamate*.
- **Chlorzoxazone** (Paraflex), acts at the spinal level,may turn urine color to red.
- **Cyclobenzaprine**(flaxeril),has a chemical structure similar to Tricyclics.
- **Methocarbamol**(Robaxin),CNS depressant, may turn urine to Brown.
  - Indicated in musculoskeletal conditions as an adjunct to rest and physical therapy.

# Corticosteroids

- Pain relief is presumably related to reduced peritumoral edema and inflammation with consequent relief of pressure and traction on pain sensitive structures, in addition to euphoric and increased appetite in some patients.
- Indicated in acute pain (raised ICP and cord compression) and chronic pain such as the one related to spread of bulky tumor.
- May be useful adjunct in Status Migrainous and is often very effective for short term use in prevention of Cluster headaches.

# Biphosphonates and Calcitonin

- Mainly indicated in bone Pain caused by Osteoclast-induced bone resorption by tumor.
- Biphosphonates , **Etidronate** and **Pamidronate** are analogues of endogenous pyrophosphates which inhibit bone resorption in vivo.
- **Calcitonin**, is also potent inhibitor of Osteoclast- induced bone resorption.

# Neuroleptic agents

- D2 receptor antagonism is associated with clinical potency of these drugs (**High Potency-Haldol, Perphenazine, Low Potency- Chlorpromazine**).
- Side effects include sedation, hypotension anticholinergic and extrapyramidal side effects such as Neuroleptic malignant syndrome, dystonia, akathisia, rigidity, tremors and tardive dyskinesia.
- The use of Neuroleptic agents has diminished over the years except in **Deaffrentation syndromes** and agitation.

# Nonsteroidal Anti-inflammatory Drugs

- The primary mechanism of action of the NSAIDs appears to be inhibition of prostaglandin synthesis, primarily through the cyclooxygenase pathway. The leukotriene pathway, with inhibition of 5-lipoxygenase, may be affected by the NSAID **ketoprofen**.
- The concurrent use of NSAIDs may be opioid sparing. NSAIDs may have further benefit as adjuvant treatment in metastatic bone disease.

# Nonsteroidal Anti-inflammatory Drugs

- Two isoenzymes of cyclooxygenase [**COX**] have been identified. Animal data indicates that **COX-1** primarily is responsible for prostaglandins involved with “housekeeping functions,” which include gastric cytoprotection, renal vasodilatation, and vascular hemostasis.
- **COX-2** which is found in inflamed tissues, appears to be the isoenzyme responsible for the regulation of the inflammation.

# NSAIDs

- **Mild to moderate migraine and Tension headaches**
- **Exertional**
- **Orgasmic**
- **Chronic Paroxysmal Hemicrania (Indomethacin)**
- **Hemicrania continua (Indomethacin)**
- **Icepick syndromes (Indomethacin)**
- **Acute or intractable migraine (Ketorlac)**



# NSAIDs

- **Salicylates**      **Aspirin**  
(**Anacin**)   **Choline Mg**  
**Trisalicylate** (**Trilisate**)
- **Propionic Acids**  
**Naproxen**(**Aleve**)  
**Ibuprofen**(**Motrin**)  
**Ketoprofen**(**Orudis, Or**  
**uval**)
- **Indoles**  
**Ketoralac**(**Toradol**)  
**Etodolac**(**Lodine**)
- **Nonacidic** **Nabumetone**  
(**Relafen**)
- **Phenylactic acids**  
**Diclofenac** (**Voltaren**)
- **COX-2 inhibitors**  
**Celecoxib** (**Celebrex**)  
**Rofecoxib**    (**Vioxx**)  
**Valedocoxib** (**Bextra**)

# NSAIDs Gastropathy

- Risk factors include: age over 60, prior h/o PUD, Steroid use, Alcohol use, multiple NSAID use and the first 3 months of use.
- Prevention: Antacids and **Cimetidine** has limited success to be ineffective. **Sucralfate** and **Omeprazole** are generally more effective.
- **Misoprostol** PGE1 analog is the drug of choice, associated with 25% incidence of diarrhea.

# NSAIDs renal toxicity

- Renal impairment has been reported to occur in as many as 18% of patients using **Ibuprofen** whereas in other studies acute renal failure has been shown to occur in about 6% of patients using NSAIDs.
- Forms of renal impairment with NSAIDs include a reduction in **renal perfusion** due to inhibition of prostaglandin formation, acute **interstitial nephritis**, and **nephrotic syndrome**.

# Para-amino phenol

- **Para-amino phenol** derivative **Acetaminophen [APAP]** is an analgesic and antipyretic agent that lacks anti-inflammatory properties and is similar to ASA.
- **APAP** affects pain primarily through peripheral mechanisms [blockade of generation of pain impulse]. APAP may also have a central effect on nociceptive transmission by raising pain threshold or inhibition of COX 3.

# Para-amino phenol

- Hepatic damage (secondary to Glutathione depletion) after overdose of APAP is minimized with administration of N-acetylcysteine [NAC], especially when within 8 hours after the ingestion of APAP.
- Unlike the situation with ASA, there is no correlation between serum concentration and analgesic effectiveness.
- Hepatic damage may occur with daily doses of 4 to 8 gm. Hepatic damage is exacerbated in patients with a history of alcohol abuse.

# Topical local anesthetics

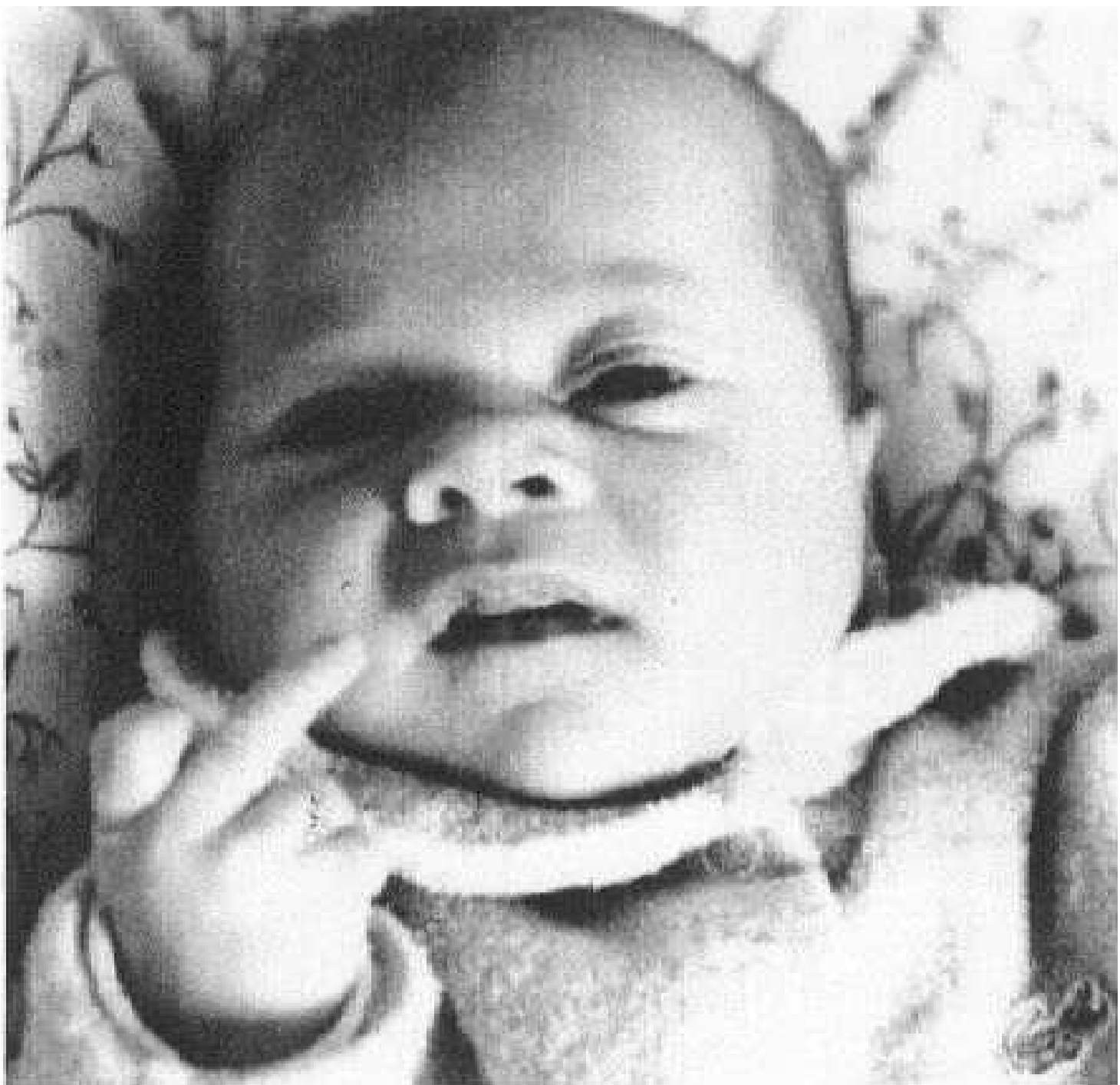
- **EMLA cream** is a eutectic mixture of amide local anesthetics, **Lidocaine 2.5%** and **Prilocaine 2.5%** formulated as an oil-in-water emulsion.
- The amount absorbed is determined by the area over which it is applied and the duration of application.
- **Lidocaine 5%** patch is FDA approved for PHN peak level is 0.13 ug/ml on average dosages.

# Capsaicin

- **Capsaicin** (**Zostrix**) is a topical analgesic. It may inhibit the synthesis, transport and release of substance P.
- It is used in the treatment of pain associated Neuralgia, Neuropathic pain and Arthritis.
- Therapeutic effects appears after 6 to 8 weeks of continuous application.
- Some susceptible patients may also experience wheezing, sneezing, or asthma-like symptoms at exposure to the drug.









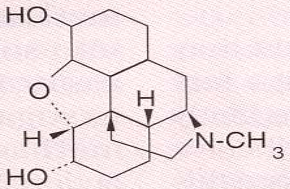
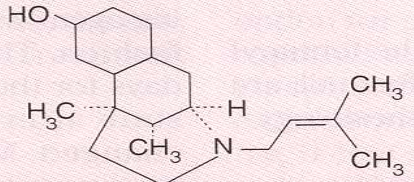
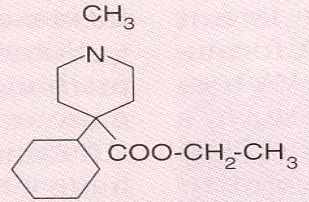
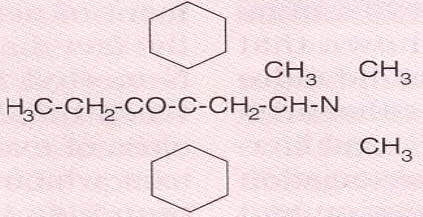
# Weak Opioids

- **Tramadol** (Ultram)
- **Propoxyphene** (Darvocet)
- **Codeine** (Tylenol #2, 3 and 4)
- **Hydrocodone** (Vicodin)

# Potent Opioids

- **Morphine** (Oramorph)
- **Hydromorphone** (Diludid)
- **Methadone** (Dolophine)
- **Levorphanol** (Levodromoran)
- **Oxycodone** (Percocet, Oxycontin)
- **Fentanyl** (Duragesic)



Class	Example	Agents	Cross sensitivity
Phenanthrenes	<p>Morphine</p>  <p>The image shows the chemical structure of morphine, a pentacyclic alkaloid. It features a morphine skeleton with a hydroxyl group at the 3-position, a methoxy group at the 3-position, and a hydroxyl group at the 6-position. The nitrogen atom is methylated (N-CH<sub>3</sub>).</p>	<p>Morphine Codeine Hydromorphone* Levorphanol* Oxycodone* Oxymorphone* Buprenorphine* Nalbuphine* Butorphanol*</p>	Probable
Benzomorphans	<p>Pentazocine</p>  <p>The image shows the chemical structure of pentazocine, a benzomorphan. It features a pentacyclic benzomorphan skeleton with a hydroxyl group at the 6-position, a methyl group at the 10-position, and a propenyl group at the 11-position.</p>	Pentazocine	Possible
Phenylpiperidines	<p>Meperidine</p>  <p>The image shows the chemical structure of meperidine, a phenylpiperidine. It features a piperidine ring with a methyl group on the nitrogen atom and a propyl ester group (-COO-CH<sub>2</sub>-CH<sub>3</sub>) attached to the 4-position of the piperidine ring.</p>	<p>Meperidine Fentanyl Alfentanil Sufentanil</p>	Low risk
Diphenylheptanes	<p>Methadone</p>  <p>The image shows the chemical structure of methadone, a diphenylheptane. It features a heptane chain with a carbonyl group at the 3-position and a nitrogen atom at the 7-position. The 2-position of the heptane chain is substituted with two phenyl rings. The 4-position is substituted with a methyl group, and the 6-position is substituted with a methyl group.</p>	<p>Methadone Propoxyphene</p>	Low risk

\*These agents lack the 6-OH group of morphine, possibly decreasing cross sensitivity within the phenanthrene group.



# Weak Opioids

<b>Tramadol</b>	Oral	150 mg	6-8h
<b>Propyxephene</b>	Oral	360	3-4h
<b>Codeine</b>	Oral	180	3-4h
<b>Hydrocodone</b>	Oral	30	3-4h

# Potent Opioids

<b>Morphine</b>	IV/oral	10/30 mg	3-4 h
<b>Hydromorphone</b>	IV/oral	1.5/7.5 mg	3-4 h
<b>Methadone</b>	IV/oral	10/20 mg	4-8h
<b>Levorphanol</b>	IV/oral	2/4 mg	4-8h
<b>Oxycodone</b>	oral	30 mg	3-6h
<b>Fentanyl</b>	TD	25 ug=60-90 mg po MS	72 hr

# Agonist Antagonists

- **Buprenorphine**(**Buprenex** )
- **Butorphanol** (**Stadol**)
- **Dezocine** (**Dalgan**)
- **Nalbuphine** ( **Nubaine**)
- **Pentazocin**(**Talwin**)

# Mechanism of action

- Opioids act as agonists to specific Opioid receptors present at presynaptic and postsynaptic sites in the central and peripheral nervous system.
- Opioid receptors belong to superfamily of Guanine-Protein coupled receptors.
- Binding sites are categorized as mu, kappa and delta receptors.
- Levorotatory isomers are the most active.



# Classification of Opioid Receptors

- **Mu-1(Endorphins)**
  - Analgesia, Euphoria, Miosis, N/V, Urinary retention and Pruritis
- **Mu-2**
  - Analgesia, sedation, Hypoventilation, Bradycardia and ileus
- **Delta (Enkephalins)**
  - Modulation of mu receptor activity.
- **Kappa(Dynorphins)**
  - Analgesia, Sedation, Dysphoria and Diuresis

# Opioid receptors

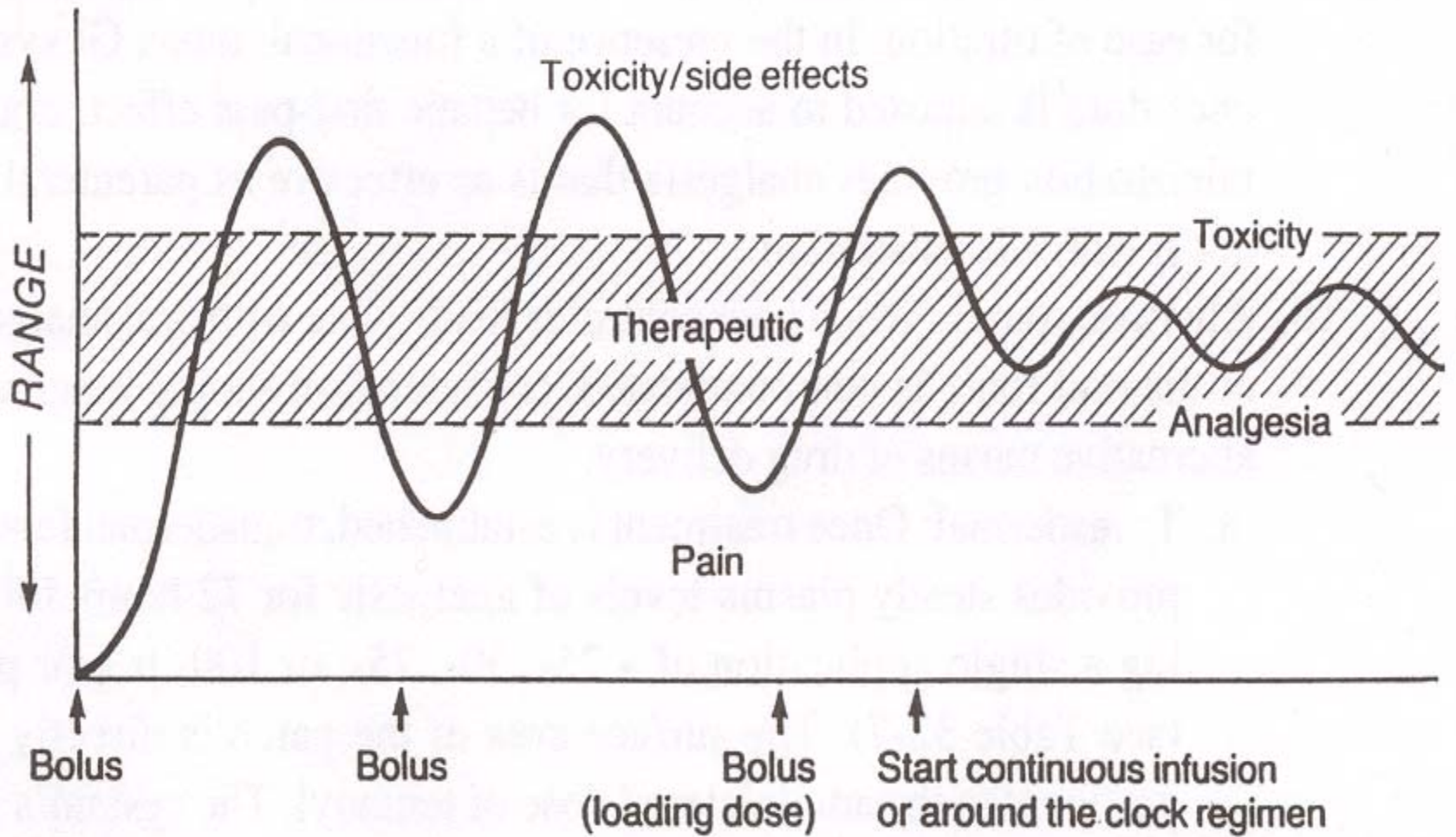
- Activation of Opioid receptors inhibits the Presynaptic release of excitatory neurotransmitters from terminals of nerves carrying nociceptive activity .
- Placement of Opioids in the subarchnoid or Epidural space is based on knowledge that opioid receptors are present in the **Substantia gelatinosa** of the spinal cord.

# Metabolism

- **Morphine has three metabolites M3G, M6G and Normorphine. M3G is the major metabolite, which lacks analgesic properties. Less than 1% of Morphine is excreted in the urine. An estimated 33% of administered dose of Morphine undergoes nonurinary, non hepatic metabolism.**
- **Meperidine undergoes extensive N-demethylation to Normepidine.**
- **After n-dealkylation, Oxycodone is metabolized to Noroxycodone and Oxymorphone.**

# Routes of administration

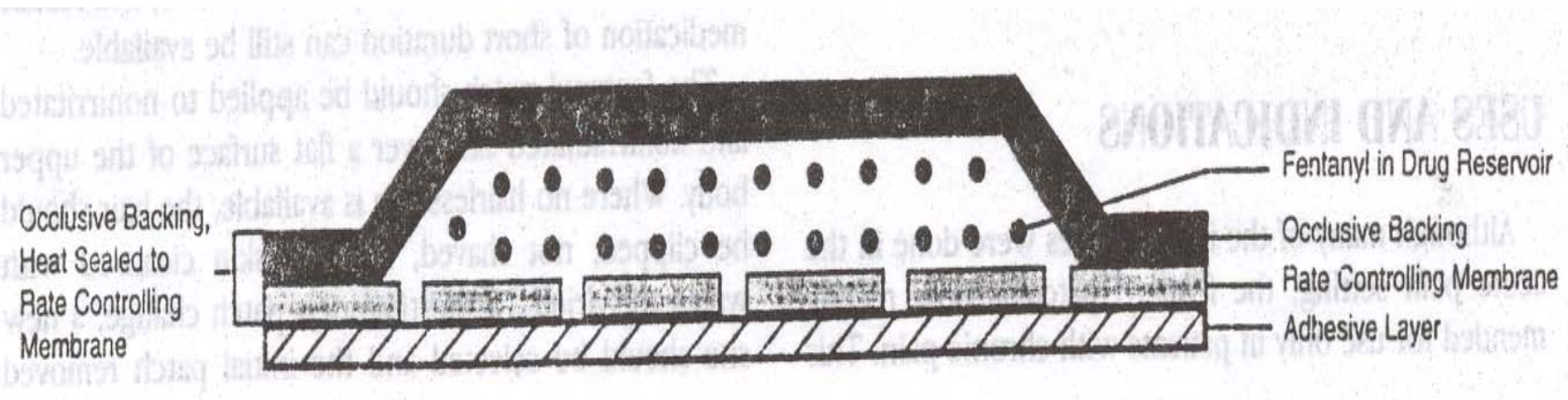
- **Oral**
- **Subcutaneous**
- **Sublingual**
- **Intravenous**
- **Transdermal**
- **Rectal**
- **Intrathecal**
- **Epidural**



# Fentanyl patch

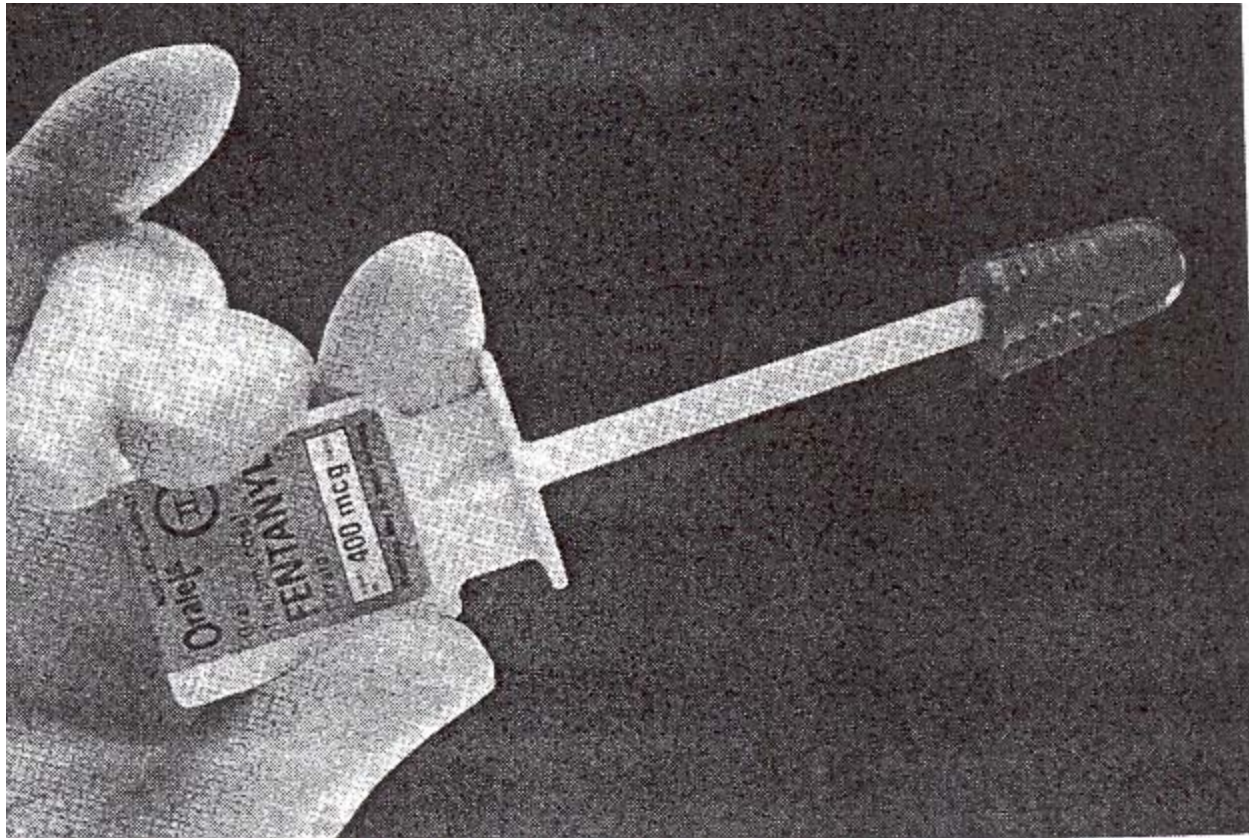
- Transdermal fentanyl provides steady plasma levels of analgesic for 72 hours following a single application of a 25, 50, 75 or 100 ug/hr patch. The surface area of the patch is directly proportional to the administered dose of Fentanyl.
- Temperature is the most important factor that influences the rate of absorption.
- Peak level is achieved after 12 to 18 hours

# Fentanyl patch





# Oral Transmucosal Fentanyl





# **Methadone**

- **Powerful analgesia**
- **NMDA antagonistic activity**
- **Long Half life**
- **Less Euphoric than morphine**
- **less street value than Morphine**
- **Very inexpensive**

# Side Effects of Opioids

- **Constipation**
- **Nausea and vomiting**
- **Sedation**
- **Urinary retention**
- **Respiratory depression**
- **Spasm of sphincter of Oddi**
- **Drug interactions**
- **Opioid induced Hyperalgesia**

# Nausea and vomiting

- Occur in up to 50 % of patients first exposed to an Opioid and after dose increases. These Symptoms usually resolve spontaneously with continued use.
- Stepwise therapy : 1-Initially a Major Tranquilizer (Prochlorperazine (compazine), Promethazine (phenergan)) should be used. 2-A Prokinetic agent (Metoclopramide or Cisapride) If gastric stasis is present or 3- Scopolamine if related to ambulation.  
4-Ondansetron, Dronabinol and corticosteroids for refractory N/V. and 5- Trial of alternative Opioid analgesic.

# Constipation

- **Opioid induced constipation is sufficiently common that it should almost be treated prophylactically.**
- **Stepwise therapy :** 1-Initially increase fluid and fiber intake 2-Stool softener is prescribed when opioid therapy commences (Docusate or mineral oil) 3-Stimulant Laxative (Senna or Castor oil)4-Bulk Laxative (Lactulose or Psyllium).5-Manual disimpaction .

# **Tolerance, Dependence and Addiction**

- **Tolerance, the need for increasing dosages over time to maintain a desired effect.**
- **Physical Dependence is a state characterized by the onset of withdrawal symptoms when a drug is precipitously stopped.**
- **Addiction is 1- psycho-behavioral phenomenon with possible genetic influences resulting in a-  
overwhelming drug use. 2-non medical drug use and continued use despite the presence or threat of physiologic harm.**

# Opioid-induced Hyperalgesia

- **Mechanism might be related to increased sensitivity Of NMDA receptors to excitatory Amino Acids.**
- **Similar Mechanisms implicated in Opioid tolerance.**
- **Discontinuation of Opioids may actually lead to reduction in Pain.**

# Drug interactions

- Serotonin syndrome when MAOI interact with **Meperidine**.
- Adverse Depressive drug interactions has been described with Fentanyl secondary to accumulation of the opioid, which produces respiratory depression, hypotension and coma.

# Tramadol

- **Tramadol(Ultram)**: Tradamol is an atypical centrally acting analgesic with uniquely independent dual mechanism of action. Dual analgesic activity is provided by both centrally acting supraspinal opioid activity and a secondary mechanism associated with monoamine reuptake inhibition.
- The **Tramadol** racemic mixture produces two enantiomers, each of which has a different spectra activity